Synthesis of Partially Saturated Bicyclic Heteroaromatics: sp^3-Enriched Scaffolds for Drug Discovery

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31st July 2018

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This dissertation is submitted for the degree of Doctor of Philosophy

Declaration

This dissertation is submitted in fulfilment of the requirements for the degree of Doctor of Philosophy. It describes work carried out in the Department of Chemistry, University of Cambridge, between October 2014 and July 2018 under the supervision of Prof. David Spring. Unless otherwise indicated, the research described is my own and not the product of collaboration. The work presented in this dissertation has not been submitted for any other degree. It does not exceed the prescribed word limit for the Physics and Chemistry Degree Committee.

Signed,

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Abstract

Recent years have seen an expansion beyond the more druggable biological targets into novel areas of biological space. However, drug discovery campaigns against these challenging targets have been afflicted with low hit rates during screening campaigns and high levels of candidate attrition during clinical trials. Subsequent studies have looked to explore the underlying factors to these challenges and have identified the lack of scaffold diversity and poor physicochemical properties in screening libraries as the leading causes.

In an attempt to address this issue drug discovery strategies such as fragment-based drug discovery and lead-oriented synthesis have been developed which control and direct the compound properties within screening libraries towards relevant areas of chemical space. In addition, strategies such as diversity-oriented synthesis aim to synthesise structurally complex and diverse compounds, expanding screening collections into previously under-explored areas of chemical space.

This thesis reports the development of a step-efficient, modular and highly adaptable synthetic route for the synthesis of partially saturated bicyclic heteroaromatic scffolds (Figure i). The designed route takes advantage of the large chiral pool provided by amino acids, with each scaffold synthesised in just 4-6 steps from these readily available enantiopure starting materials. The mild conditions allow for excellent functional group tolerance, thus enabling the incorporation of growth vectors for chemical elaboration from the outset, a strong advantage in the drug discovery process.

Overall, 29 partially saturated bicyclic heteroaromatic compounds were synthesised based around 7 different scaffolds. These demonstrated a number of possible areas for diversifation both on and around the scaffold, including variation of functional groups (Figure i, red), double (*cis*-diastereoisomers) and single (R_2- and R_3-positions) substitution patterns, variation of the 5-membered heterocycle (Figure i, green) and increased size of the saturated ring (Figure i, blue). Furthermore, careful selection of the substituents, heterocycle and size of the saturated ring would enable the synthesis of screening libraries within the constrainsts of fragment-like, lead-like or drug-like structures.

The final library has been incorporated into the Diamond XChem high-throughput crystallography program and initial screening has identified a weakly binding hit for Activin A.

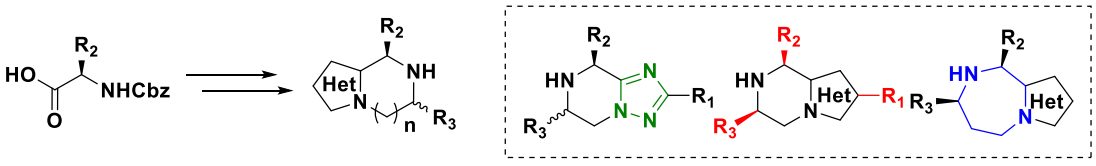

Figure i: Demonstrating the partially heteroaromatic scaffolds targeted and the possible points of diversity.

Acknowledgements

Firstly, I would like to thank my supervisor, Prof. David Spring for giving me the opportunity to undertake this PhD and for offering his advice and support throughout the last 5 years. I would also like to thank Tom Moss for his helpful advice and extensive chemistry knowledge, as well as for his supervision during my time at AstraZeneca. I am grateful to AstraZeneca for the CASE award.

My thanks go out to all Spring Group members past and present, who have not only always generously offered their help and advice, but also made the last 5 years a truly wonderful experience, in the lab, the Alma and beyond. In particular, to Hannah Sore, who has kept me going through the tough times and always has excellent pearls of wisdom. To Warren Galloway, who has supported me throughout my time at Pembroke and who encouraged me to apply to the Spring group all those years ago. To Twigg, whose help and supervision during the first year, and more recently with the proof reading of this thesis has been invaluable. To Joe, who despite his best efforts did not manage to dissuade me from staying with Chemistry and who has been a fantastic friend and supporter for the last 5 years. To Steve and Stephen, for always persuading me to go for one large glass of Rosé, often more than one. To Sarah for always having a listening ear, Tommy and Gabri for their ability to answer all of my stupid questions and all of my proof readers for putting up with and correcting my terrible typos and flying commas: Warren, Gabri, Twigg, Hannah, Sarah, Steve and Josie.

Camilla and Matt deserve a special mention for joining me as the last 3 standing at Pembroke. To all the PCBC and Cantabs Senior Women's members past and present who have given me many great memories and the perfect escape out on the river, with some wins and some loses which I will never forget.

Finally, and most importantly, I would like to thank my family, without whom none of this would have been possible. My grandparents get a special mention, Grandad for continually despairing of my ever leaving university and contributing some taxes towards his pension and Granma for sustaining my studies and research with door steps of bread pudding and for always being on the end of the phone. Thanks to Kelsie and Niall for putting up with me, and Tilly for listening to all my woes, without judgement or comment. However, the person without whom none of this would have been possible is Mum, our hour long phone calls keep me sane and I run out of words, rare I know, when it comes to your support during so many crises and low moments. Thank you for never giving up on me and for never letting me give up.

For Mum

Abbreviations

°C - degrees Celcius

Ac - acetyl

ADMET - adsorption, distribution, metabolism, excretion, toxicity

aq - aqueous

APT - attached proton test

ARE - antioxidant response element

BIOS - biology-oriented synthesis

Bn - benzyl

Boc - *tert*-butoxycarbonyl

br - broad

Bu - butyl

CAN - cerium ammonium nitrate

cat. - catalytic/catalyst

Cbz - carboxybenzyl

CLL - chronic lymphocytic leukaemia

cm^{-1} - wavenumbers

CMC - comprehensive medicinal chemistry

COE - cyclooctene

COSY - correlation spectroscopy

Cp - cyclopentadienyl

d - doublet

CH_2Cl_2 - dichloromethane

DIPEA - *N*,*N*-diisopropylethylamine

DLS - Diamond Light Source

DME - dimethoxyethane

DMF - *N*,*N*-dimethylformamide

DMP - Dess-Martin periodinane

DMSO - dimethylsulfoxide

DOS - diversity oriented synthesis

EDC - 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

eq. - equivalents

Et - ethyl

FBDD - fragment-based drug discovery

FDA - US Food and Drug Administration

FT - fourier transform

g - gram(*S*)

GSK - GlaxoSmithKline

h - hour(*S*)

H-bond - hydrogen bond

HAC - heavy atom count

HATU - *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide

HBA - hydrogen bond donor

HBD - hydrogen bond donor

HBTU - *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate

HMBC - heteronuclear multiple bond connectivity

HMQC - heteronuclear multiple quantum coherence

HOAt - 1-hydroxy-7-azabenzotriazole

HOBt - hydroxybenzotriazole

HPLC - high pressure liquid chromatography

HRMS - high resolution mass spectrometry

HTS - high throughput screening

Hz - hertz

IBX - 2-iodoxybenzoic acid

IC_{50} - half maximal inhibitory concentration

ID - identification

IR - infrared

J - coupling constant

KHMDS - potassium bis(trimethylsilyl)amide

L - litre(*S*)

LCMS - liquid chromatography-mass spectrometry

LDA - lithium diisopropylamide

L.E. - ligand efficiency

Lit. - literature

m.p. - melting point

m - multiplet

m - *meta*

M - molar

mCPBA - *meta*-chloroperoxybenzoic acid

Me - methyl

min - minute(*S*)

mg - milligram(*S*)

mL - millilitre(*S*)

mmol - millimole(*S*)

MOE - Molecular Operating Environment

mol% - mole percent

MW - molecular weight

NBS - *N*-bromosuccinimide

NCE - new chemical entity

NME - new molecular entity

NMM - *N*-methylmorpholine

NMR - nuclear magnetic resonance

NOESY - nuclear overhauser spectroscopy

p - *para*

PCA - principle component analysis

PG - protecting group

Ph - Phenyl

PLS-DA - partial least squares discriminant analysis

PMB - *para*-methoxybenzyl

PMI - principle moments of inertia

PPI - protein-protein interaction

ppm - parts per million

pTSA - topological polar surface area

q - quartet

R & D - Research and Development

RBC - rotatable bond count

R_f - retention factor

rt - room temperature

SAR - structure-activity relationship

TEA - triethylamine

Tf - triflic

TFA - trifluoroacetic acid

THF - tetrahydrofuran

TLC - thin layer chromatography

TMS - trimethylsilyl

VEHICLe - virtual exploratory heterocyclic library

wt% - weight percent

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1. Introduction

1.1. Drug Discovery Process and Challenges in the Pharmaceutical Industry

Over the last 20 years, the pharmaceutical industry has seen a reduction in revenue, the approval of ever fewer new chemical entities (NCE's) each year and a decrease in the quality of research and development (R & D) pipelines.[1–3] In fact, clinical candidates are more likely to fail now than in the 1970s with only 1 in 10 eventually marketed.[4,5] These symptoms highlight the significant decline within the industry, the causes of which are widely considered to be complex and intertwined.[1–3] Despite this, some changes within the industry have coincided with the decline and are therefore considered contributing factors: (i) a strong aversion to risk, (ii) addressing more challenging targets, (iii) increasing R & D costs, (iv) escalating clinical trial costs, (v) high levels of attrition during late-stage clinical trials, (vi) changes in the regulatory landscape and (vii) increased entry of generic drugs into the pharmaceutical market.[6,7]

The process of drug discovery is lengthy and expensive with multiple stages, typically spanning 12-15 years and costing over $2.6 billion.[5,8] Target identification and validation begins the process: for a particular disease state, a biological target must be identified and the link between target modulation and clinical outcome demonstrated. This usually involves the use of so-called chemical probes or tool compounds to inhibit the target and study the outcome, thus delivering an understanding of the biological pathways and target(s) associated with the studied disease state. A lack of a thorough understanding of the pathways studied can result in target modulation failing to have the desired clinical outcome when tested during clinical trials (Figure 1.1).[6]

Once a target has been validated, compound screening is used to identify molecules with the desired activity ('hits'). Once a series of hits is identified they are refined into 'leads': potent and selective compounds with adequate pharmacokinetic properties for *in vivo* testing.[5] These leads are then further optimised to improve potency and drug-like properties such that potent and selective preclinical candidates with good pharmacokinetic and pharmacodynamic properties can be identified.

The preclinical candidate will then be subjected to safety and efficacy testing using both computer modelling and *in vivo* animal testing prior to entering human clinical trials. Phase I clinical trials are usually carried out on healthy volunteers, with the primary aim of assessing the safety and side effects of the drugs to thus determine an optimal dose. If a candidate is successful through phase I, phase II clinical trials are the point at which it will first be tested in patients with the disease, thus the first 'proof

of concept' studies are carried out. This is the most common point of failure in the drug discovery process. The final stage of clinical trials, phase III aims to ensure that the candidate is effective and safe for long term use.

Upon successful completion of phase III clinical trials, the clinical candidate can then be registered and marketed.

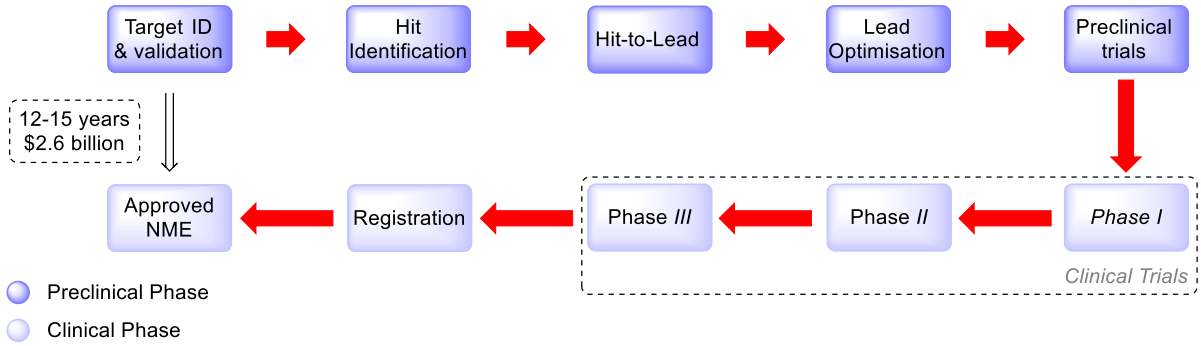


Figure 1.1: The drug discovery process: ID = identification; NME = new molecular entity. Figure adapted from reference.[9]

1.2. Screening Strategies, the Nature of Screening Libraries and Downstream Effects

Drug discovery projects can and do fail at every stage of the long and arduous process outlined in Figure 1.1. However, the nature of the library used for the initial screening is widely considered to be of central importance in this regard, since the outcome of this stage impacts upon all downstream phases.[1–3,6,10,11] The hit rate provided by a library is clearly significant, however, the quality of these hits is also a crucial consideration. High quality hits are generally considered to be those that can be efficiently optimised to generate lead compounds with improved efficacy and safety.

Traditionally natural products have been a major source of new drugs; they are highly diverse with specific biological activity, proposed to be a result of their inherent receptor binding capacity. However, natural products are often difficult to source and challenging to identify, purify and chemically modify and this limits their use in screening libraries. Chemical synthesis has therefore dominated the generation of small molecule screening libraries, with the composition of the screening library dependent upon the screening strategy employed.[5]

1.2.1. High Throughput Screening (HTS) of Combinatorial Libraries of drug-like small molecules

High throughput screening techniques involve the rapid automated screening of thousands to millions of compounds to identify those with some degree of affinity for the target, and as such is currently the most widely used technology for identifying hits for drug discovery.[12] It first came to prominence in the late 1980s, as a result of the development of combinatorial chemistry methods which enabled chemists to produce very large numbers of compounds in an efficient manner though the systematic and covalent linkage of various building blocks.[13] The prevailing belief of the pharmaceutical industry at the time was that drug discovery was just a 'numbers game'[4,14] and, as such, it was assumed a plethora of new drug leads would be generated as a consequence of the sheer numbers of molecules being screened.[15] Disappointingly, this hypothesis did not prove to be successful and the low hit rates, alongside the high levels of failure during phase I of clinical trials, led to the development of a number of guidelines to improve the molecular properties of screening compounds. The first of these, which is still widely used today, is Lipinski's 'rule of five'.[16] It was developed in the early 1990's to overcome the poor physicochemical properties which were believed to contribute to approximately 40% of failures in Phase I clinical trials.[3]

Lipinski *et al.* used experimental and computational approaches to study the effect of physicochemcial properties on solubility and permeability in a drug discovery setting,[16] resulting in four guidelines for oral bioavailability: 5 H-bond donors or fewer, 10 H-bond acceptors or fewer, molecular weight (MW) below 500 and calculated log P (Clog P) of 5 or less. It was suggested that violation of more than one of these guidelines would result in compounds with poor oral absorption and therefore poor pharmacokinetic and oral bioavailability properties causing likely attrition in phase I of clinical trials.[16] Lipinski's 'rule of 5' guidelines were quickly and widely implemented in HTS libraries; and fortuitously, this reduced the attrition rate due to poor ADMET (adsorption, distribution, metabolism, excretion, toxicity) characteristics to just 10%.[3,10]

Unfortunately, despite Lipinski's efforts, HTS is still afflicted with issues as demonstrated by the low hit rates seen in the hunt for novel antibacterial drugs. GlaxoSmithKline (GSK) evaluated over 300 bacterial genes and identified 160 essential targets between 1995 and 2001. They ran a total of 70 screening campaigns, including 67 HTS campaigns and 3 whole cell screens each with over half a million small molecules and a cost of $1 million. The initial results were disappointing with only 16 hits of which only 5 were developed into lead compounds, with the remainder unable to meet the required criteria, even after chemical modification. None of the 5 leads were carried forward due to: (i) a lack of antibacterial activity despite target modulation; (ii) some non-specific toxicity as a result of indiscriminate cell-membrane disruptions; (iii) a lack of the broad spectrum activity desired; and, (iv) insufficient drug-like properties.[17] Of the hundreds of antibacterial screening campaigns run worldwide, only 2 compounds were identified with sufficient potency, antibacterial activity and broad spectrum activity for a novel target.

This low hit rate is unsustainable.[18–20] Whilst it has primarily been attributed to insufficient or improper molecular diversity in the screening libraries, the poor developability and inappropriate chemical properties of hits and leads also highlights the need for new criteria for screening library compounds.[4,12,17–22]

1.2.2. Compound Properties in Screening Libraries

Despite the implementation of Lipinski's 'rule of 5', attrition of compounds in clinical trials is as prevalent as ever. However, the most common point of failure has shifted from phase I to phase II, which now has only a 25% success rate (Figure 1.2).[2] Whilst ascribing a single reason to compound failure could be considered an oversimplification, phase II clinical trials are the point at which 'proof of concept' studies are first carried out and as a result, failure can often be attributed to lack of efficacy and safety issues.[2,3,6,10,11]

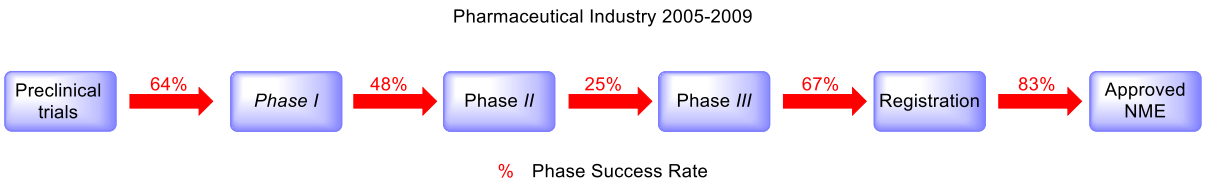


Figure 1.2: Demonstration of the success rate of clinical candidates, using data from 14 large pharmaceutical companies between 2005 and 2009 (Abbott, AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis and Schering-Plough). Data from the Pharmaceutical Benchmarking Forum (hhtp://kmrgroup.com/ForumsPharms.html). Approval data based on approval by a regulatory authority in a major market (EU, US or Japan). Figure adapted from reference.[2]

Given that at each stage of drug discovery there is an associated increase in overall cost of development, this late-stage failure poses a significant problem, and it is crucial to develop paradigms and methodologies to identify risk pre-clinically, and therefore limit late-stage failures and the associated costs.[3] To this end, a number of studies have been carried out exploring the causes behind both efficacy and safety failures; physicochemical properties are found to be significant in both.[1,6,10,11,23]

Efficacy-related attrition is multi-faceted, with poor biological validation and poor compound properties both significant contributing factors. The safest and most potent drug will still fail if target modulation does not give the required outcome, however when considering screening libraries, it is the failures due to compound properties that are most important. AstraZeneca estimated that 29% of efficacy failures could be attributed to compound properties, such as pharmacokinetic properties, as the compounds exposure to the target tissue could not be established.

Safety issues are associated with promiscuity (off target interactions) and mechanism-based toxicity (unforeseen adverse effects due to on-target interactions). Whilst toxicity due to either will result in project failure, a study by AstraZeneca looking at the fate of their drug pipeline suggested that 75% of safety failures were related to compound properties.[6] This ties in with a number of studies suggesting a link between compound properties and toxicity due to promiscuity.[6,10,11,24,25] Given the complexity of biological systems large data sets are required to establish any kind of meaningful correlation between compound properties and toxicological outcomes.[10] However, in general, an increased probability of failure is linked to the increased promiscuity of highly lipophilic compounds.[10]

In an attempt to quantify this, a study from Pfizer using animal toxicology data found that if compounds had clog P greater than 3 and topological polar surface area (tPSA) less than 75Å^2 they would be 2.5 times more likely to have off-target toxicity.[25] In contrast, in animal studies AstraZeneca's found no correlation between compound-related toxicological attrition and clog P and PSA within the ranges studied (clog P: 1-6 and pTSA 30-120Å^2). However, partial least squares discriminant analysis (PLS-DA) found that increased sp^3 atom count in pre-clinical candidates diminished toxicity attrition.[24] The difference in these two studies could be down to methodology or library composition, however, it does

highlight how subjective and context dependent these studies can be, especially when using averaged or categorised data which can exaggerate the strength of correlations.[10] Thus whilst it is important to take heed of the studies, it could be suggested that applying specific guidelines too rigorously might be counterproductive. At the same time, whilst highly lipophilic and aromatic compounds are likely to give higher hit rates, they will also be more promiscuous and their prevalence in screening libraries should therefore be limited to reduce toxicity related attrition.

1.2.3. Aims for the Future of Drug Discovery

HTS campaigns that employ these traditional combinatorial libraries are typically found to be associated with low hit rates (percentage of screening library identified as active) and low hit quality (that is, the suitability of hits for continued optimisation) and therefore, those hits that are developed into clinical candidates often suffer high levels of attrition during the later stages of the drug discovery process.

Furthermore, the 'low-hanging fruit' within drug discovery have already been well studied, and thus only the more challenging targets remain.[2] Some of these have historically been deemed "undruggable", such as protein-protein interactions (PPIs),[15] whilst others are only just coming to light as a result of advances in molecular biology. One such family which has become an important target area within medicinal chemistry is that of epigenetics. The epigenome comprises over 230 enzymes and recognition proteins involved in epigenetic regulation of gene expression and therefore has significant clinical applications in the field of oncology amongst others.[2,26–28] The human proteome is vast, and many of the biological targets within it have never been identified or studied, with all marketed drugs estimated to target fewer than 500 biomolecules.[12]

To attempt to modulate these novel targets, a shift in the composition of screening libraries needs to take place, not only to increase the structural diversity within the libraries but also to improve their compound properties: lowering lipophilicity and aromaticity and increasing the saturation of compounds. In recent years, in an attempt to address these complex issues a number of screening paradigms and strategies for library synthesis have been developed.

In the rest of this introduction, the importance of structural diversity within libraries and these approaches to drug discovery will be discussed.

1.3. Structural Diversity in Drug Discovery

Chemical space is vast, with an estimated 10^{60} possible organic molecules with up to 30 carbon, nitrogen, oxygen or sulphur atoms[29] and since it is impossible to sample all of it, the huge conundrum within drug discovery is which regions of chemical space to explore.[30] One way to guide the exploration of chemical space is the principle of chemical diversity.[31]

Chemical diversity is an intuitive concept that can be measured in a wide variety of ways using a number of different molecular properties.[31,32] The chemical diversity of a library depends almost entirely on the descriptors, metrics and multivariate methods used to assess it.[33] Physicochemical and topological descriptors are common properties used in chemical diversity studies, however,[33] structural diversity is most common within the remit of medicinal chemistry. With respect to small molecules, structural diversity generally incorporates four principle components:[34–36]

1) *Appendage diversity* (or building block diversity): variation in different structural moieties attached to a common molecular skeleton;
2) *Functional group diversity*: variation in the functional groups present;
3) *Stereochemical diversity*: variation in the spatial orientation of potential macromolecule-interacting elements; and
4) *Scaffold diversity*: presence of multiple distinct molecular skeletons (scaffolds).

The scaffold is considered to be the core molecular framework that provides the basic shape, rigidity or flexibility of the molecule and can be used therefore to represent a compound collection.[37,38] It also defines the three-dimensional spatial arrangement of the various substituents on its periphery. As such, the scaffold controls the alignment of the functional groups, determining whether they are positioned in a way that enables molecular recognition and interaction with the biological target. Scaffold diversity is, therefore, generally regarded to play the most significant role in determining the overall structural diversity of a small molecule set and can be considered the most important feature of a screening library. It is therefore an important factor in determining the success of screening endeavors.[35,39–41]

1.3.1. Scaffold Diversity in Drug Discovery

The term ‘scaffold’ is very subjective, and there exist multiple ways of defining it. In general they entail abstracting or decomposing the drug framework into simpler sub-structural elements (Table 1.1, Figure 1.3).

These varied approaches, whilst valid and widely used within studies, will give subtly different pictures of library diversity due to the use of different scaffold definitions or different data sets.

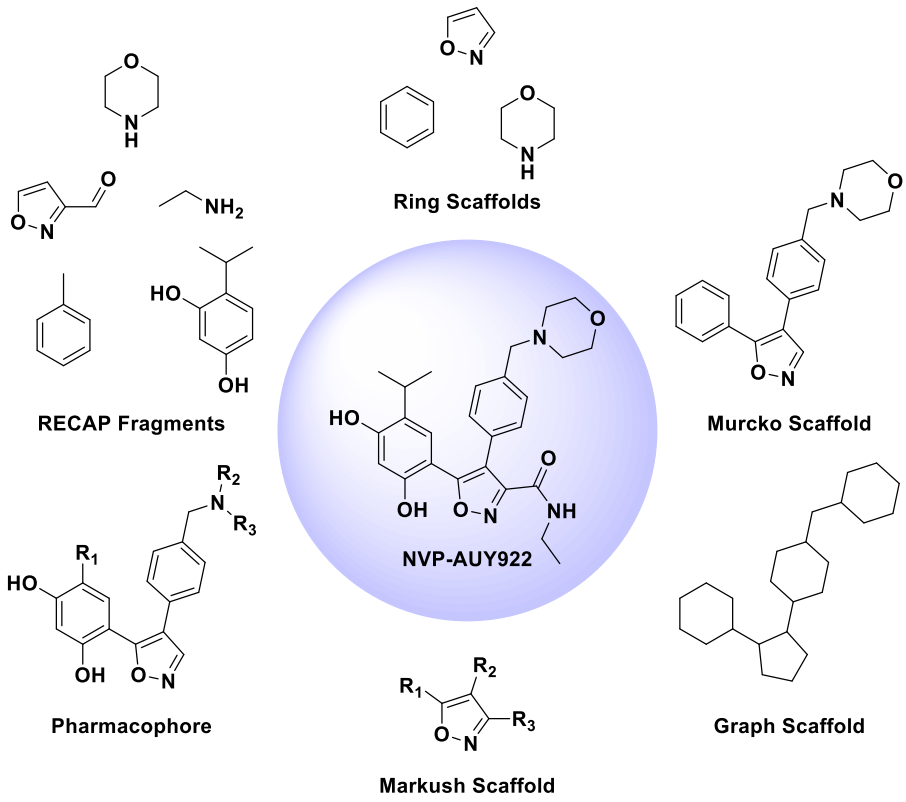


Figure 1.3: Illustration of the different scaffold representations using the HSP90 inhibitor NVP-AUY922 as an example. Figure adapted from reference.[42]

Table 1.1: Definitions of different scaffold representations.

Scaffold Representation	Definition
Maximum common substrate (MCS)	For a group of molecules clustered according to their chemical fingerprint, atom-by-atom matching is used to identify the largest common substructure for the cluster. Hence this method is entirely dependent on the dataset chosen, therefore not illustrated in Figure 1.3. [42,43]
Largest Rigid Fragment/ Ring System	The scaffold is considered to be the largest central cyclic system, with smaller ring substituents not considered.[44,45]
Murcko's Scaffold	Scaffolds derived from molecules by removing side chains and preserving the atoms in the ring system or linking rings systems and the sp^2 atoms directly bonded to these atoms. As outlined by Bermis and Murcko.[42,46,47]
Graph Scaffold (Cyclic skeleton concept - CSK)	Follows the same principles as Murcko's scaffold, however, all appendages are removed and all non-carbon atoms are converted into sp^3 carbons, thus a range of equivalent scaffolds are represented which vary in only their heteroatom substituents. [48]
Markush Scaffold	Generic structures generated by using R groups to denote the substitution patterns, thus enabling a single scaffold representation to encode multiple scaffolds.[42,49]
Retrosynthetic Combinatorial Analysis Procedure (RECAP)	Molecular frameworks described by fragmenting molecules around bonds which are formed by common chemical reactions.[33,50]
Pharmacophore	The medicinal chemistry definition of a scaffold, constituting the core scaffold that is responsible for the biological activity through interaction with the target. [42]

A number of studies have been carried out utilising these different definitions of a scaffold to analyse the diversity of existing drugs and compound librraies. A general trend appears in which most librraies have an over-representation of a small number of scaffolds, and that there is a distinct lack of scaffold diversity in the field of medicinal chemistry as a whole.[31,33,39,40,42,46,47,50,51]

The comprehensive medicinal chemistry (CMC) database is a database of the structures and properties of known drugs; in 1996, Murcko and Bemis used this to analyse the scaffold diversity at the Murcko scaffold and graph scaffold levels. They found that when using a graph framework, the 5120 compounds were comprised of 1179 unique graph scaffolds, of which just 32 scaffolds accounted for 50% of the total compounds, whilst 783 (66%) of the frameworks were found in only a single drug molecule. Even when using the more complex Murcko scaffolds (considering the atom type, hybridisation and bond roder), only 41 frameworks accounted for 24% of the drug molecules.[46]

Lipkus *et al.* took this analysis one step further by analysing a much larger dataset, and not restricting their analysis to drug molecules. They used a subset of almost 25 million compounds from the CAS registry, a database of approximately 33 million known chemical substances from the literature.[52] As with the analysis by Bemis and Murcko, they looked at both the simple graph scaffolds and the Murcko scaffolds, and the lack of scaffold diversity became even more apparent with the larger dataset analysed. The dataset was idenitifed as representing 2.5 million Murcko scaffolds and 0.8 million graph scaffolds. Considering the more complex Murcko scaffold it was found that 5% of these scaffolds were found in 75.5% of compounds, meaning approximately 1.3 million frameworks occur in a single compound. Unsurprisingly, this becomes even more drastic at the simpler graph scaffold level, with just 0.2% of frameworks occurring in 70% of compounds and 47% of graph scaffolds having a single exemplar compound (Figure 1.4).[31]

This in-depth analysis highlights that within chemical space a small number of scaffolds are playing a dominant role, which truly highlights the lack of scaffold diversity in current drug discovery efforts.

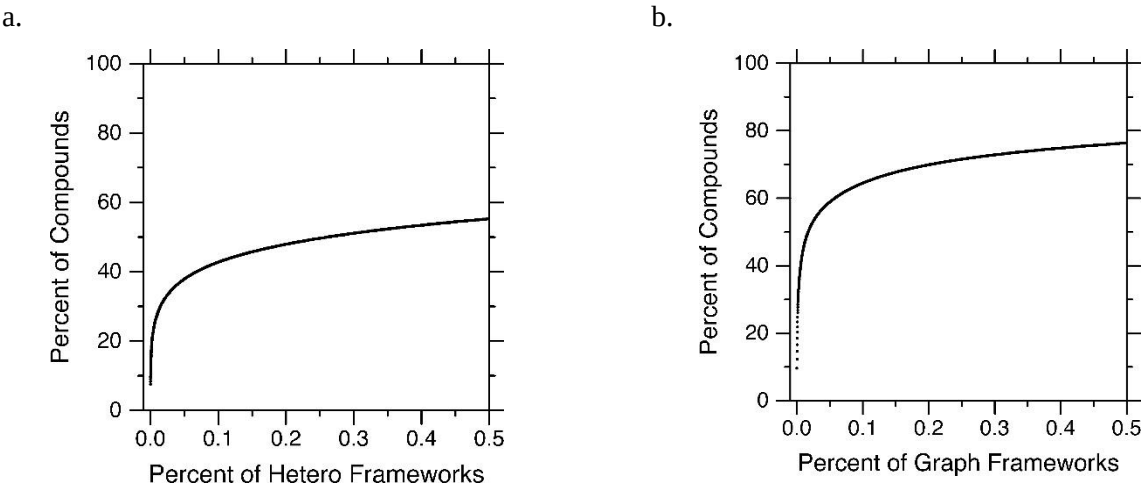


Figure 1.4: Graphs illustrating the percentage of compounds containing a particular percentage of scaffolds: a. using the Murcko scaffold definition; b. using the graph scaffold definition. They both show a greatly expanded x-axis, since the vast majority of compounds are represented by very few scaffolds. Figure taken from reference.[31]

1.3.2. Rings in Drug Discovery

Ring systems play an essential role as drug scaffolds. They give the molecules their fundamental shape and affect their flexibility as a result of having fewer degrees of freedom than non-cyclic systems. Furthermore, they are important for the positioning of substituents in three-dimensional space.[51,53] The composition of ring systems can also play an important role in the global characteristics of molecules due to their electronic properties and hydrophobicity, and it is these global characteristics which are important for the bioavailability, metabolic stability and toxicity of the molecule when in a drug discovery setting.[51] This is highlighted by a number of studies exploring the prevalence of rings within the pharmaceutical industry: although the exact values vary depending on the subset of compounds analysed, it is found that between 95 and 97% of bioactive or drug molecules contain at least one ring system, with 95% containing 6 rings or fewer and only 5.9% containing a single ring.[31,51,53,54]

However, as with scaffold diversity more generally, as discussed in the previous section, within the sub-set of rings there is an over-representation of a small number of scaffolds, with 83% of the ring scaffolds found in natural products not represented among commercial molecules.[55] Furthermore, compared to natural products, ring scaffolds within screening libraries have fewer fused, bridged or spiro-ring systems, further limiting the structural diversity and complexity.[56]

When looking more closely at the distribution of ring types an analysis by Ertl *et al.* found that 75.6% of the bioactive molecules studied contained at least one aromatic ring, whilst 65.2% contain at least one aliphatic ring.[51] Analysis by Roughley *et al.* found an even more extreme 99% of the compounds analysed contained an aromatic ring.[57] This varies substantially from the proportions found in natural products, for which only 37.9% contained an aromatic ring compared to 73.2% with an aliphatic ring.[51] Given the inherent biological activity in natural products, this disparity therefore supports the current trend for an increase in the fraction of sp^3 atoms in ring systems in drug discovery,[53,58–61] and this can only be assisted by a move away from library construction using traditional combinatorial chemistry methods, in which 80% of ring systems generated were found to be aromatic.[62]

Indeed flat compounds dominate combinatorial libraries; 71% of library members will not have a single chiral centre. The bias towards aromatic rings seen within the current and historic drug market is generally considered to be as a result of their commercial availability and more robust chemistry compared to three-dimensional scaffolds. The development of metal-mediated cross-coupling reactions, such as Suzuki and Sonogashira, and Friedel Crafts acylation and alkylation makes synthesis and modulation of scaffolds around aromatic rings simple and efficient compared to saturated rings. For aliphatic rings there is the added complication of the need to control stereo- and regiochemistry when carrying out modifications, and as a result, carbon-carbon bond forming reactions are far less common, with an over-reliance on modification through the heteroatoms.[53,57]

Many studies suggest more three-dimensionality in screening library compounds will improve both the diversity of the screening library and their ADMET properties: thus providing a better starting point for the drug discovery process.[53,59] By saturating an aromatic scaffold, there is not only an increase in complexity as a result of the increased three-dimensionality, there is also the possibility of increased structural diversity since for a very small increase in molecular weight there is the potential for significantly more isomers, this can be seen when comparing dimethylpiperidine and dimethylpyridine (Figure 1.5).[59] From the other end of the drug discovery process, an increase in three-dimensionality has been shown to improve both the solubility and developability of compounds for drug discovery.[59,63–67] It has been suggested that ideally, screening libraries should be diversified by inclusion of more representative exemplars of singleton scaffolds and more three-dimensional scaffolds.[42]

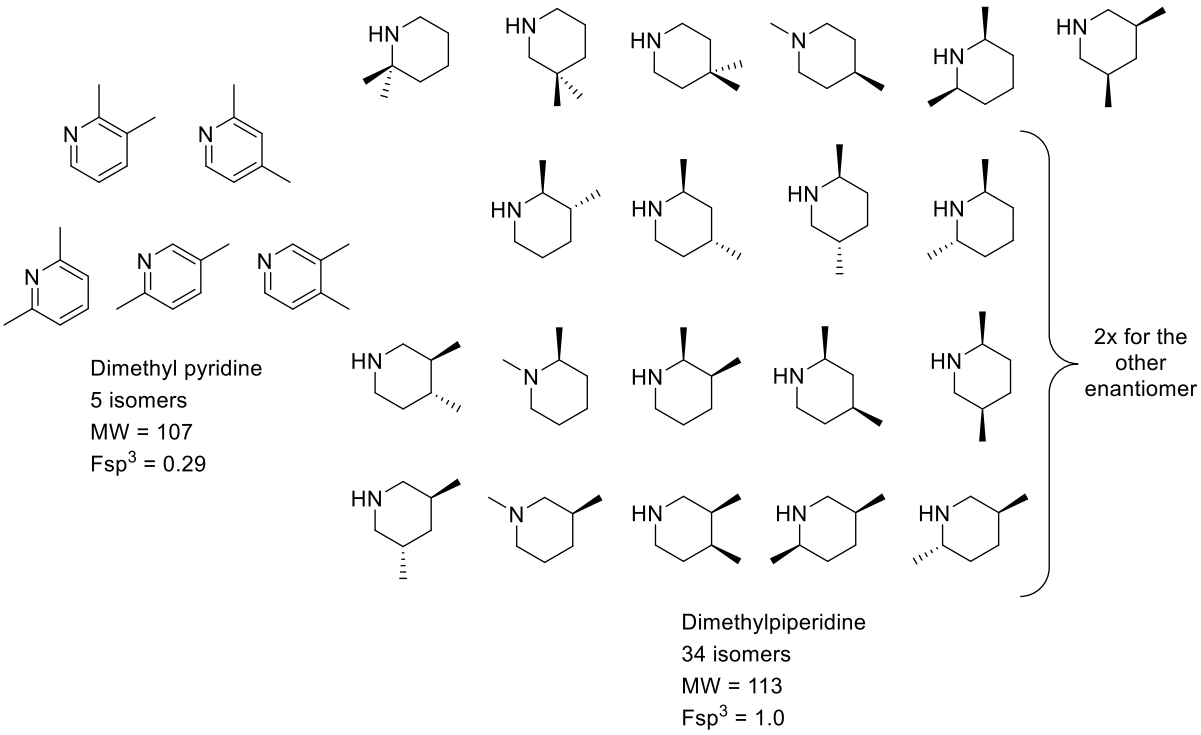


Figure 1.5: Isomers of dimethyl pyridine and dimethylpiperidine. This illustrates that a slight increase in molecular weight can enable access to significantly more isomers and the compounds accessed have greater three-dimensionality than their pyridine counter-parts. Where Fsp^3 is the fraction of total carbons which are sp^3 hybridised. Figure modified from reference.[59]

1.3.3. Heterocyclic Scaffolds

The analysis carried out by Lipkus *et al.* (Section 1.3.1) also found that 98.6% of Murcko scaffolds within the CAS registry contained at least one heteroatom.[31,54] When applying this to rings, it is found that heteroaromatics are a dominant class of rings within bioactive molecules, often directly involved in interactions with receptors either through heteroatoms *via* hydrogen bonds, or through hydrophobic interactions.[51] Their lack of flexibility reduces the entropic penalty of binding and their hydrogen bonding abilities can offer high levels of target selectivity. Synthetically, aryl-aryl couplings and the aromatic nature of heteroaromatics can enable rapid exploration of substitution patterns.[68] However, they are not without their disadvantages. Their lack of flexibility can be a double edged sword, advantageously reducing the entropy penalty whilst simultaneously restricting structure-activity relationship (SAR) studies to a single plane. In a similar manner, the hydrophobic nature and flat shape can also result in low aqueous solubility, and the synthetic tractability can result in rapid inflation of the molecular weight, which will prove counter-productive further down the line. [68]

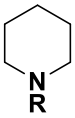
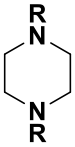
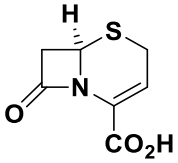
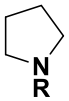
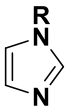
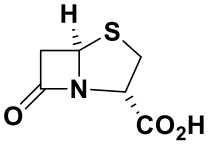
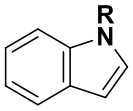
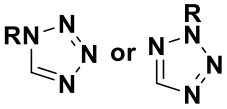
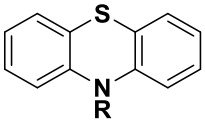
Of particular importance within the class of heterocycles are nitrogen heterocycles. In an analysis of the pharmaceuticals available in 1994, 1086 unique small molecule drugs (84%) were found to contain at least one nitrogen atom and 59% contained at least one nitrogen heterocycle (Table 1.2). These figures

far surpass the 26% and 13% seen for sulphur and fluorine respectively.[69] More recently, in 2013, 80% of the top twenty best-selling brand name drugs were identified as containing a nitrogen hetercycle.[70] As discussed, there has been an over-emphasis within combinatorial chemistry on aromatic rings, and this trend is maintained with nitrogen based heterocycles, particularly when considering 5-membered rings, of which 62% are aromatic. Whilst only 28% of 6-membered nitrogen heterocycles are aromatic, the remaining aliphatic systems predominantly consist of unsubstituted piperidine and piperazine rings, demonstrating little scaffold diversity. Also surprisingly, fused rings are seen in just 14% of drugs, despite their propensity in natural products. [69,70]

As illustrated, heterocyclic rings dominate within marketed drugs, particularly, nitrogen-based heterocycles. As a result, the most synthetically tractable ring systems already have a strong presence in marketed drugs, making novelty for patenting difficult. Thus, there is a need to explore novel heteroaromatic scaffolds.

Of the possible 23,895 unique aromatic ring systems, as predicted by Pitt *et al.* using the virtual exploratory heterocyclic library (VEHICLe), only 1701 were found to have been synthesised and published in the literature, which comprises just 7%.[68] Just 5-10 novel aromatic heterocyclic scaffolds are estimated to be synthesised and published each year, and these estimates are falling year on year.[68] This is, therefore, an important under-explored area especially given the importance of rings, and in particular heteroaromatic rings, within drug discovery. It is necessary to extend the horizon into novel heteroaromatic chemical space as well as more complex heteroaliphatic space.[68]

Table 1.2: Table showing the top 12 most common nitrogen heterocycles and their frequency in 640 nitrogen heterocycle containing small molecule drugs on the market in 1994.[69]

Number	Heterocycle	
72		Piperidine
62		Pyridine
59		Piperazine
41		Cephem
37		Pyrrolidine
30		Thiazole
24		Imidazole
22		Penam
17		Indole
16		Tetrazole
16		Phenothiazine
16		Pyrimidine

1.4. Beyond 'Traditional' Combinatorial Libraries

Chemical synthesis provides chemists with the tools needed for the synthesis of novel scaffolds with new properties, and thus it is necessary to develop a systematic approach to the application of these tools to library construction.[39] When considering composition, a balance is required between scaffold diversity and representation.[42] Dense coverage of a small number of scaffolds provides thorough coverage of pharmacophore space for a target, but will have limited scaffold diversity. Conversely, sparse representation of a large number of scaffolds can be advantageous for screening against novel targets; however once hits have been identified, hit confirmation and rapid generation of SAR can be challenging from a library of singular examples.[42]

To this end, a variety of synthetic approaches have evolved to address the problems associated with the use of 'traditional' combinatorial-type libraries through the *de-novo* synthesis of small molecule collections.[71] Most of these look to avoid the mass synthesis and screening dogma which underpinned early combinatorial chemistry,[71] instead seeking to create maximally diverse and biologically relevant libraries.[40] Two such approaches that have evolved are:[71]

1) the identification and targeting of biologically relevant chemical space, since compounds within these regions will have an increased probability of containing bioactive compounds. Methods which fall within this remit include privileged structure synthesis[72] and biology inspired synthesis (BIOS),[73] both of which focus on the synthesis of libraries based around the core scaffolds of known biologically active molecules;[14]
2) the interrogation of wide and novel regions of chemical space within a single library of small molecules. Examples of this non-biased synthetic approach to library synthesis come from diversity-oriented synthesis (DOS)[74] and DNA-encoded library technology, which combines split-pool synthesis with DNA-encoding to rapidly generate diverse libraries of compounds, each of which is encoded by a DNA tag.[75,76]

1.4.1. Targeting Biologically Active Chemical Space

In 1988 Evans *et al.* noted that certain "privileged structures" were capable of providing useful ligands for multiple receptors.[72] Evans predicted that careful modification of these privileged scaffolds could provide ligands for novel targets,[72] since privileged structures tend to already have highly favourable characteristics, and thus would provide an attractive starting point for drug discovery.[77] Although there are no hard and fast rules which define a structure as privileged, they were typically found to contain two or three ring systems connected by a single bond or fused together and are often inspired by, or derived from, natural products (Figure 1.6).[77,78] The key to privileged scaffold library construction is

the development of reactions of broad scope combined with intelligent library design such that the compounds generated incorporate appropriate drug-like properties.[79]

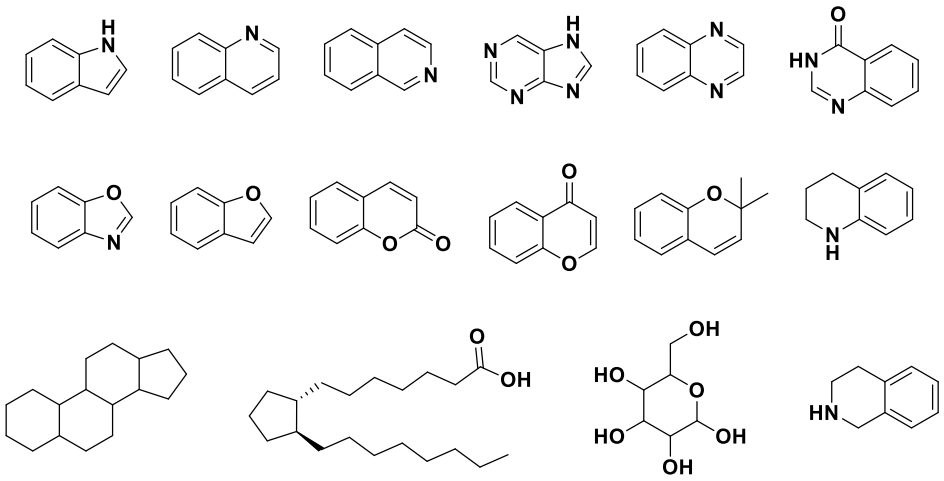
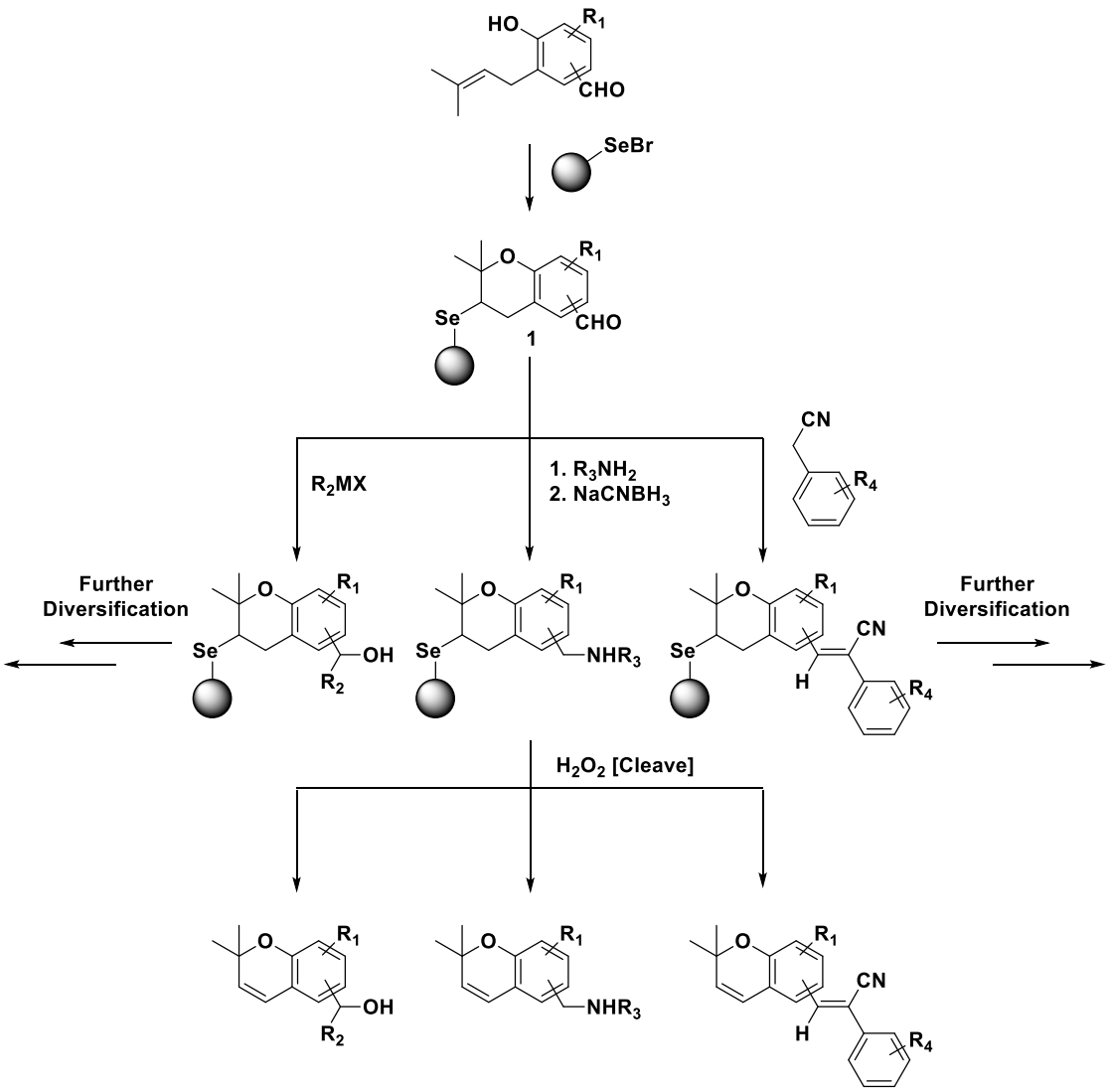


Figure 1.6: Examples of privileged scaffolds elucidated from natural products and drugs as revealed by Welsch et al.[79]

An example of the synthesis of a library based on a privileged scaffold comes from the Nicolaou group, based around the 2,2-dimethylbenzopyran scaffold **1** (Scheme 1.1).[80] The Nicolaou group developed a novel strategy that enabled them to systematically modify the entire skeleton, such that the rigidity of the heterocyclic core was maintained, but an entirely diverse natural product-like library of 10,000 members was generated. In addition they ensured that the library members maintained drug-like properties, with molecular weights between 200 and 600 and 3-6 heteroatoms per compound. Preliminary results from biological studies suggest that these library members are cell-permeable and capable of high-affinity interactions with biological targets. A number of hits have been identified, one of which has been carried forward for several rounds of additional structure-activity relationship studies.

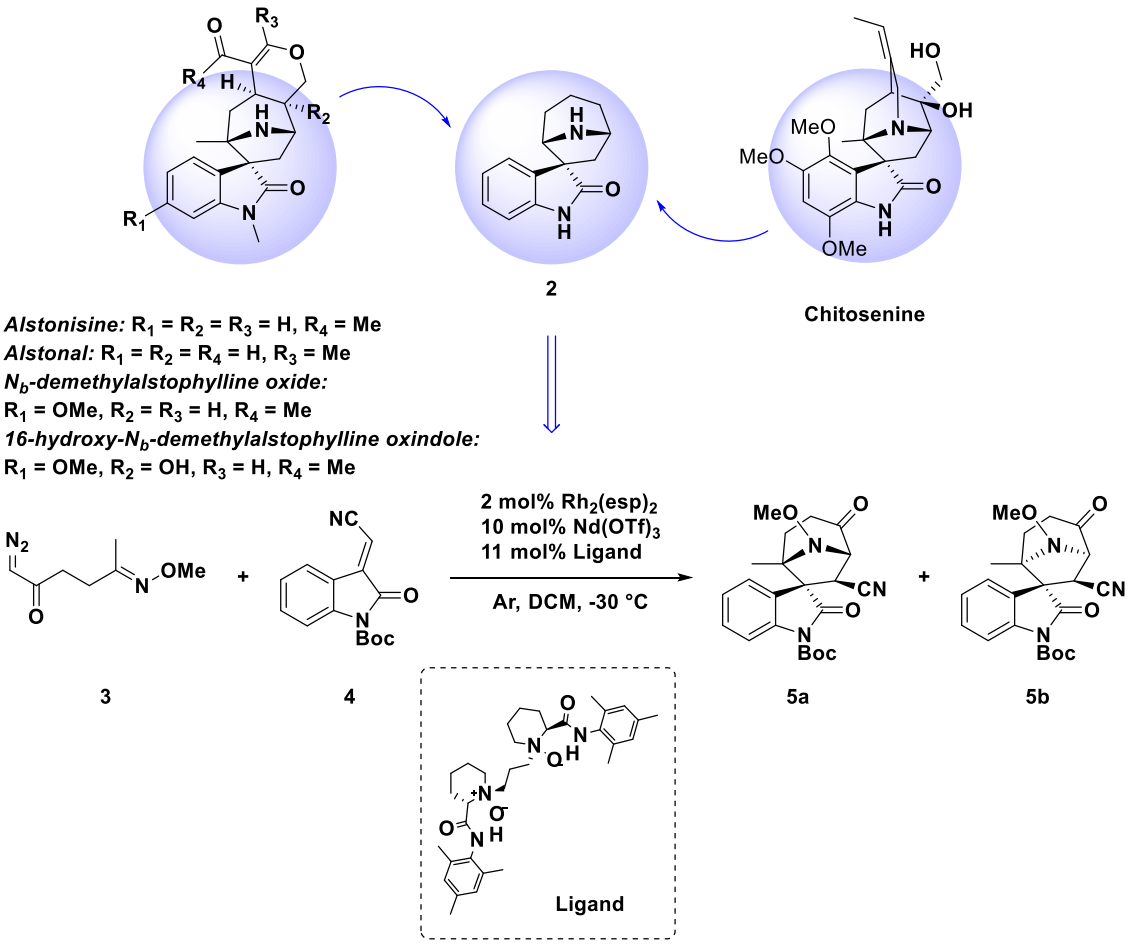


Scheme 1.1: Strategy developed by NIcolaou's Group for the development of a natural product-like library of 10,000 compounds based on the privileged scaffold of 2,2-dimethylbenzopyran ***1****. Nine aldehyde containing compounds were immobilised on a phenyl selenium resin before diversity generating reactions, such as organometallic additions to generate alcohols, reductive aminations to provide amines and Knoevenagel condensations to afford α,β-unsaturated compounds, were carried out. Each of these could then be further diversified or cleaved from the resin using hydrogen peroxide via a cyclisation sequence which removed all traces of the selenium since it might otherwise affect biological studies. Figure adapted from reference.*[80]

In a similar vein, Waldmann *et al.* developed the concept of biology-oriented synthesis (BIOS) which also takes into consideration the conservation within proteins. Despite over 10^{390} unique amino acid combinations of 300 residues being possible,[81] of the 10^4-10^5 proteins or fewer encoded for within an organism, there are often highly conserved subdomains, and so a limited number of possible small molecule binding sites. Hence, the underlying principles of BIOS are: i) natural products have an inherent ability to bind and modulate the activities of multiple protein targets, with many natural products sharing a common scaffold with the varied substitution patterns providing the specificity.[80-82] As such, the scaffolds of natural products can be assumed to define evolution-driven "privileged

structures";[72] ii) the arrangement of the secondary structure of the amino acid sequence of a protein determines its three-dimensional structure. Sub-folds within these protein structures, in turn, determine the size and shape of their ligand-binding sites, with the chemical properties of the site determined by the amino acid residues exposed. It is this amino acid variation that provides specificity for the binding of ligands, and the shape of the sub-fold which selects the three-dimensional shape of the ligand required, as determined by its scaffold.[73,85]

A recent example of the synthesis of a BIOS library is illustrated from Jia *et al.* which describes the enantioselective synthesis of a library of spirotropanyl oxindole scaffolds **2** through bimetallic relay catalysis (Scheme 1.2).[86] Spirotropanyl oxindoles were chosen due to their common incorporation into alkaloid scaffolds which can exhibit potent vasorelaxant, antiplasmodial and ganglionic-transmission-inhibiting activity.



*Scheme 1.2: Illustration of the spirotropanyl oxindole scaffold **2** within natural products and their enantioselective biology-oriented synthesis. This employs first a rhodium catalysed intramolecular carbenoid transfer from the α-diazo ketone to the ozime in **3**, followed by a 1,3-dipolar cycloaddition between the rhodium generated azomethine ylide and the 3-alkenyl oxindoles **4** in which the enantioselectivity is induced by the interaction between **4**, Nd^{III} and the chiral N,N'-dioxide ligand, such that the exo product **5a** is the major one.*[86]

As with all scaffolds, it seems highly probable that there are dozens of privileged scaffolds yet to be defined.[79]

1.4.2. Targeting Broad and Novel Regions of Chemical Space

In these approaches, the aim is to access a wider range of chemical space by virtue of increased library structural diversity. One such approach is that of diversity-oriented synthesis (DOS), first conceived and developed in 2000 by Stuart Schreiber, which was born out of a desire to address the lack of structural diversity in 'traditional' combinatorial-type screening libraries.[87,88]

DOS libraries should thus efficiently interrogate large areas of chemical space, including known biologically relevant and under-explored regions of chemical space.[89] The key advantages to this approach are (i) the conversion of simple starting materials into complex and diverse scaffolds,[9] and (ii) its efficient and modular nature, whereby scaffolds are formed in typically no more than five synthetic steps.[37]

Broadly speaking, there are two basic approaches for the generation of scaffold diversity that have been employed in DOS campaigns to date (Figure 1.7):

1) Reagent-based approach in which divergent reactions are carried out on a pluripotent substrate to afford a number of different compounds with distinct molecular scaffolds; thus it is the choice of the reagents and co-substrates that dictate the stereochemical and skeletal diversity within the final scaffold.
2) Substrate-based approach; functional groups in the substrate are reacted together ("paired") so as to fold the substrate into a distinct molecular scaffold. In this approach, scaffold diversity can be achieved in one of two ways, either: i) different reaction conditions can be applied to a single densely-functionalised molecule such that multiple scaffolds are progressed from a single scaffold; or 2) a single set of reactions conditions can be used on different starting materials to furnish products based around multiple scaffolds. Irrespective of the synthetic approach, careful consideration is required on the choice of starting materials and reaction conditions.[9]

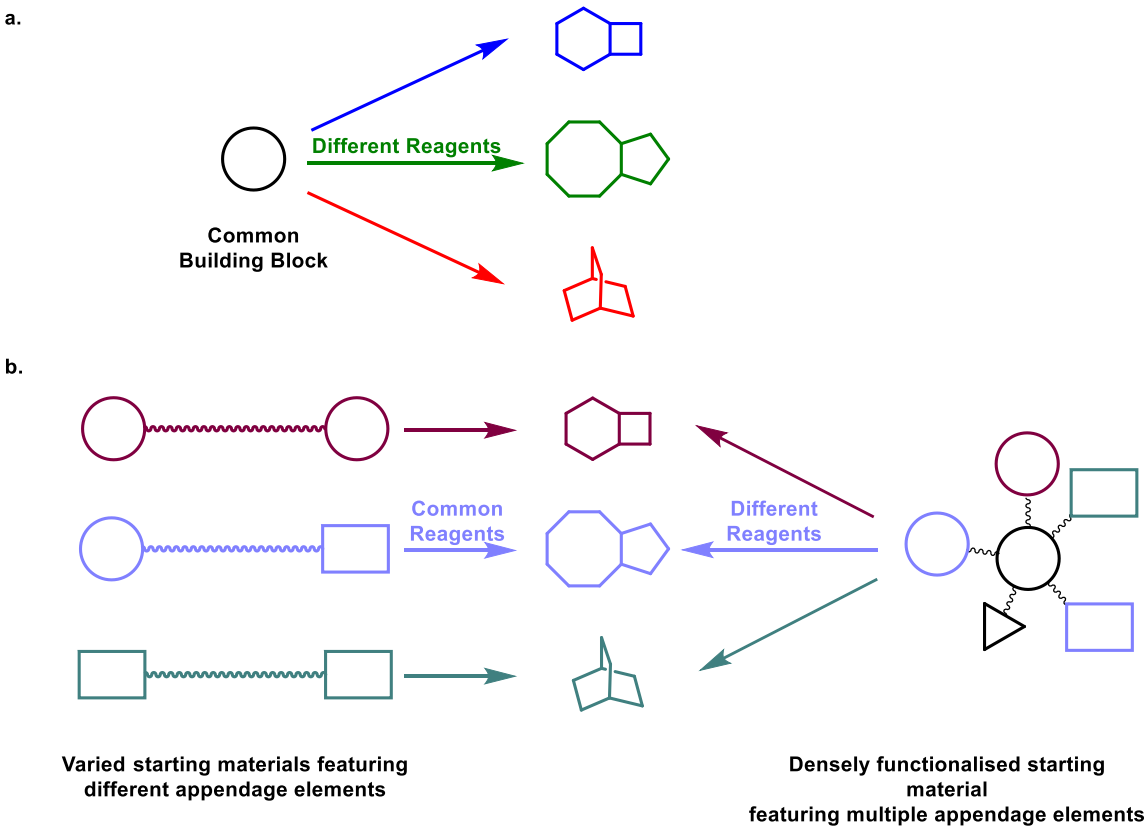


Figure 1.7: DOS strategies for the synthesis of distinct molecular scaffolds: a. reagent-based; b. substrate-based approach

These two approaches are not orthogonal and most modern DOS strategies incorporate aspects of both.[71,90,91] Other features of diversity (appendage, functional group and stereochemical) can be introduced into the compound libraries through variation in the starting materials and/or reagents used.[71,74]

A powerful synthetic algorithm that has found widespread application in DOS pathways is the three phase build/couple/pair (B/C/P) strategy (Figure 1.8).[92,93] The build phase focuses on the synthesis of building blocks containing orthogonal, and ideally some chiral functionalities. These building blocks can then be linked together, or to other substrates, in the couple phase to produce complex and densely functionalised molecules; this phase provides the basis for the introduction of stereochemical diversity. Finally, the pair phase involves the intramolecular coupling of different moieties to afford rigid scaffolds, thus installing the skeletal diversity of the library.

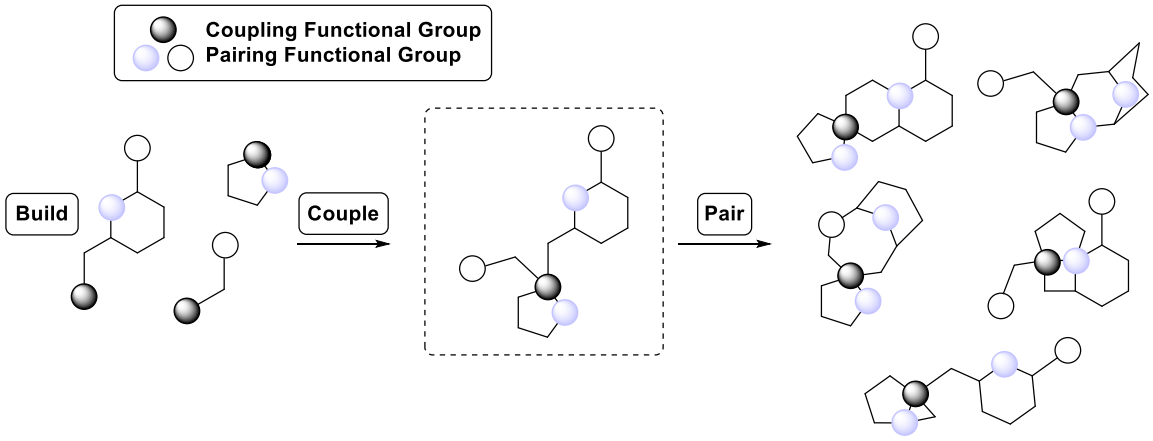


Figure 1.8: Application of DOS via Build-Couple-Pair

There are a multitude of examples of DOS campaigns resulting in structurally diverse libraries, using some or all of these strategies. A reagent-based example from the Spring group synthesised a DOS library for the development of modulators of mitosis.[94] Rhodium carbenoid chemistry was employed to produce pluripotent substrates from which a range of structurally diverse small molecules could be regio- and diastereo-selectively synthesised. Overall, a library of 35 compounds was synthesised, with 10 distinct molecular scaffolds. Computational analysis was used to generate a principal moment of inertia (PMI) plot which illustrates the shape, and therefore scaffold, diversity produced in this work. A phenotypic screen highlighted the utility of this DOS library through the identification of two library members, **19** and **20**, which caused mitotic arrest (Scheme 1.3, Figure 1.9).[94]

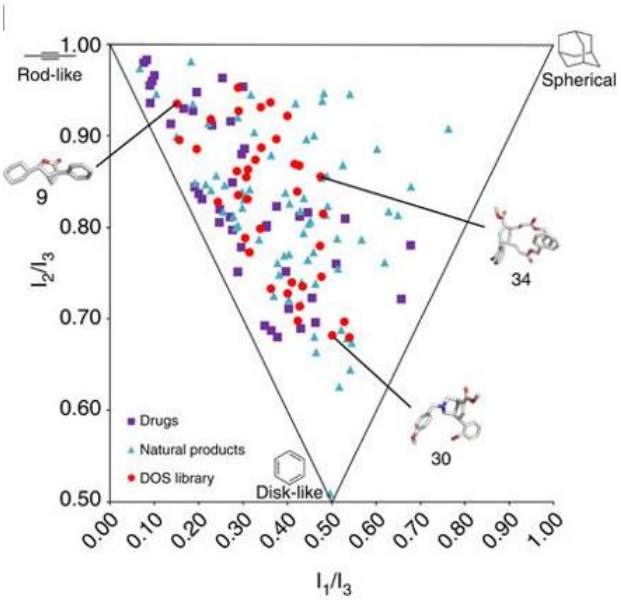
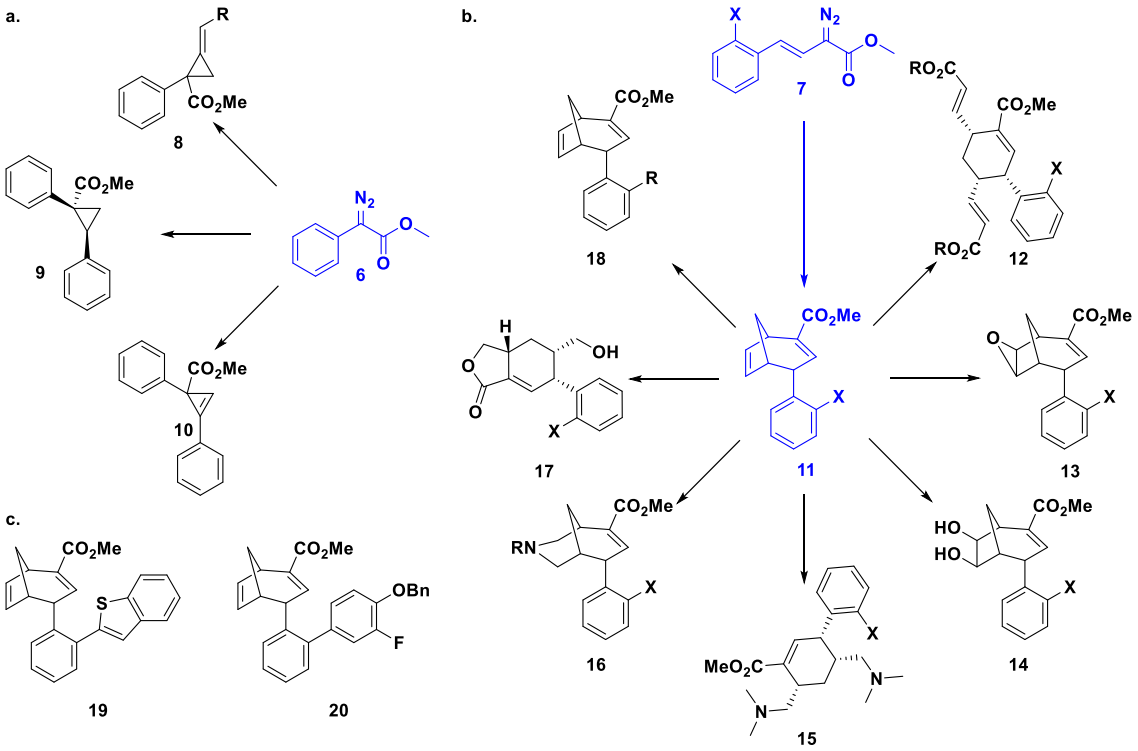


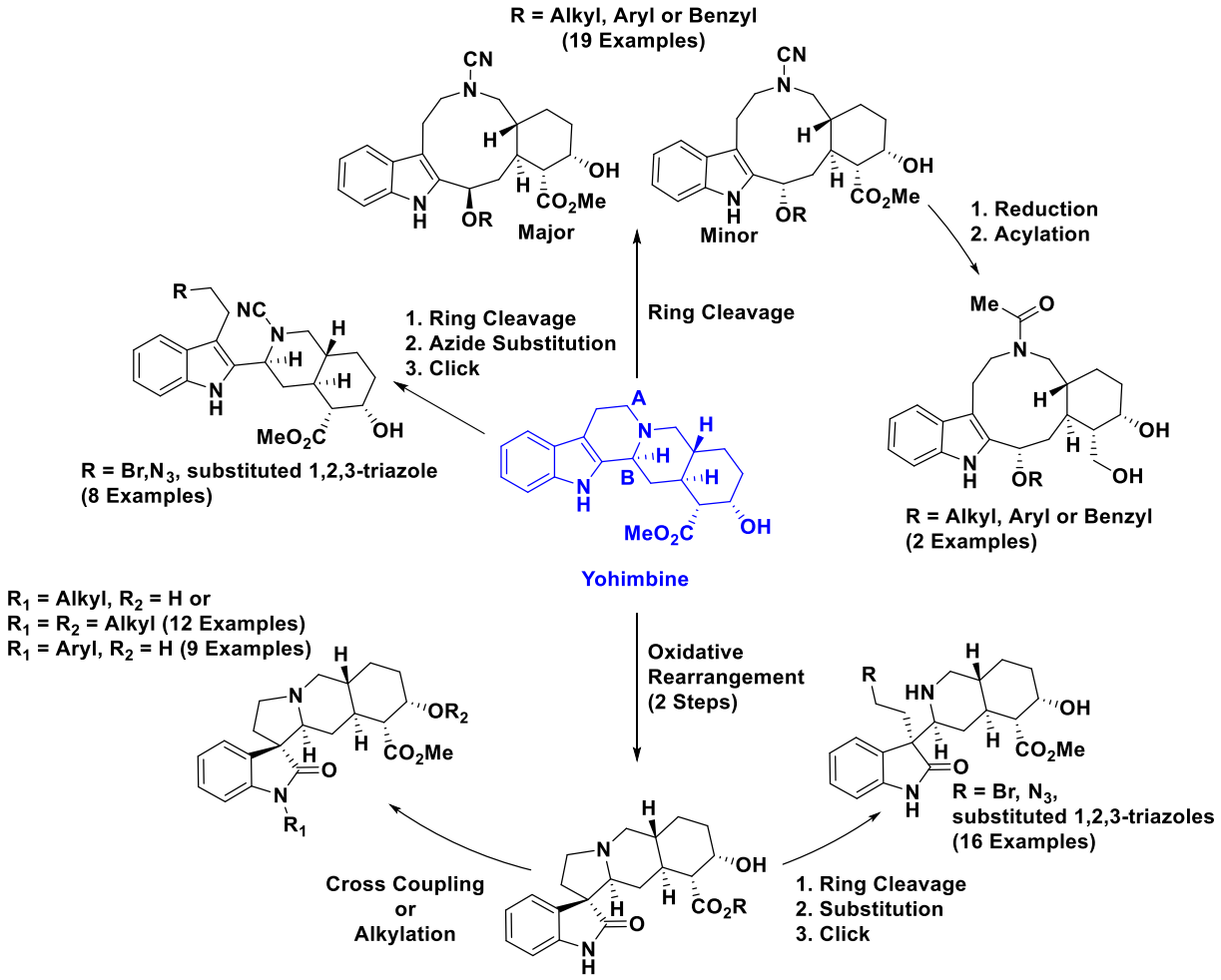
Figure 1.9: Principal Moment of Inertia (PMI) plot illustrating the degree of molecular shape diversity in the generated library of thrity-five compounds (red) compared to the top forty top-selling brand-name drugs (purple) and sixty diverse natural products (light blue). PMI is used to assess the three-dimensional shape diversity of a compound library, the individual constituents' moments of inertia along three mutually orthogonal principle axes are calculated and plotted on the triangular PMI plot.[94]



*Scheme 1.3: Example of reagent-based DOS applied to the synthesis of chemical probes for the modulation of mitosis. Phenyldiazo ester compounds (**6** and **7**) were chosen as highly functionalised substrates: a. Rhodium-catalysed cyclopropanation of **6** gave unsaturated densely functionalised compounds (**8**, **9** and **10**) which were further diversified using C-H activation reactions, lactonisations and iodolactonisations followed by radical deionisation; b. Tandem cyclopropanation-cope rearrangement of styryl diazoester derivative **7** gave highly functionalised bicycle [3.2.1]octadiene **11**. This provided ample opportunity for further diversification: including ring opening/cross metathesis **12**, stereoselective epoxidation **13**; regio- and stereo-selective dihydroxylation **14**; dihydroxylation, oxidative cleavage and reductive amination **15** (2° amines) and **16** (1° amines); dihydroxylation, oxidative cleavage, reduction and transesterification **17**; Suzuki cross couplings **18**; c. Library members which caused mitotic arrest: **19** and **20**.*

Whilst traditionally DOS has aimed to generate complex scaffolds from simple starting materials, Hergenrother *et al.* posited that the divergent modification of natural products could be employed to generate markedly different core scaffolds with novel bioactivity. This was particularly appealing since it harnessed the inherent biological activity and pre-encoded complexity of natural products and enables the rapid synthesis of novel, highly complex molecules without the lengthy syntheses usually required for natural product-like compounds. As such, this approach was named complexity-to-diversity synthesis.[95–100]

An example comes from Paciaroni *et al.* who used a tryptoline ring distortion strategy to synthesise 70 complex and diverse compounds from the complex natural product Yohimbine, an indole alkaloid (Scheme 1.4).[99] Phenotypic screening and reporter gene assays idenitified compounds with antproliferation activities against cancer cells with functional hypoxia inducible factors, nitric oxide inhibition and inhibition and activation of the antioxidant response element (ARE).



Scheme 1.4: Example of a complexity-to-diversity approach to the synthesis of a diverse library of 70 complex compounds synthesised through the ring distortion of the tryptoline scaffold in indole alkaloid Yohimbine. Ring cleavage could be used to open the central 6-membered ring at position A to generate an open ring system and at position B to form a 10-memebered central ring. Oxidative rearrangement produced a central 5,5-spirocycle at the 3-position of the starting indole fused with the 6,6-fused bicycle.[99]

1.5. Alternative Screening Paradigms

1.5.1. Lead-oriented synthesis

Traditionally, combinatorial chemistry combined with high-throughput screening aimed to identify hits from drug-like molecules. In addition to the issues associated with a lack of compound diversity discussed above, this approach tends to generate hits that have a similar molecular weight and lipophilicity as marketed drugs. Therefore physical property inflation during the optimisation process can result in the poor physical properties that result in the high rates of attrition seen.[101] Lead-oriented synthesis was introduced to address this issue by specifically targeting the synthesis of libraries of molecules with lead-like molecular properties (Table 1.3).[102]

There are a number of properties and features that should be taken into account when constructing a lead-like library to ensure maximum chance of successful drug development (Table 1.3), such as avoiding chemically reactive, electrophilic or redox active groups which are known to cause problems during drug discovery. Similarly, higher numbers of aromatic rings and lower numbers of sp^3 carbons are affiliated with poorer solubility and other undesirable properties.

Table 1.3: Table describing the molecular properties and features used to describe lead-like small molecule, [102] as compared to the drug-like small molecules.[103]

Molecular Properties and Features	Preferred Lead-like Values	Preferred Drug-like Values
Lipophilicity	$-1 < \text{clog P} < 3$	$-2 < \text{clog P} < 5$
Molecular size	$14 < \text{HAC} < 26$	$20 < \text{HAC} < 70$
	$200 < \text{MW} < 350$	$200 < \text{MW} < 500$
Number of Aromatic Rings	≤ 3	-
Complexity	Favour higher Fsp^3	$Fsp^3 = 0.47$
Substructures	Avoid molecules containing chemically reactive, electrophilic or redox active groups.	-

By restricting the molecular weight to between 200 and 350, which is the approximate equivalent of 14 to 26 heavy atoms, it becomes easier to sample broader areas of chemical space, since every additional heavy atom added to an organic molecule is estimated to increase the number of biologically relevant potential structures by a factor of 10.[104]

Most significant is the consideration given to lipophilicity. Lipophilicity essentially reflects the key event of molecular desolvation as a drug transfers from the aqueous phase to cell membranes and protein binding sites, which are usually hydrophobic in nature. High lipophilicity can therefore enable binding to multiple targets, leading to promiscuity and the associated toxicity, often resulting in attrition during clinical trials.[105] In addition, poor solubility and metabolic clearance have a strong positive correlation with high lipophilicity, causing efficacy issues and therefore also contributing to the probability of attrition. Lead-like space is therefore defined by molecules with clog P values in the range -1 to 3, since this range is considered to give the best balance of properties for oral drugs.

These guidelines are predominantly targeted at orally dosed drugs, so drugs dosed *via* alternative methods may be amenable to a wider range of physical properties. However it is proposed that lead-like molecules still represent a good starting point for optimisation, with the potential to undergo property inflation without exceeding drug-like space (Figure 1.10).[104] Unfortunately, only 2.6% of the 4.9 million compounds from commercial vendors reside within this lead-like space, and therefore novel synthetic approaches need to be developed to target this under-represented area of chemical space, in particular in a way that enables variation of the molecular scaffold in preparation for SAR studies and lead optimisation upon identification of a hit.[102]

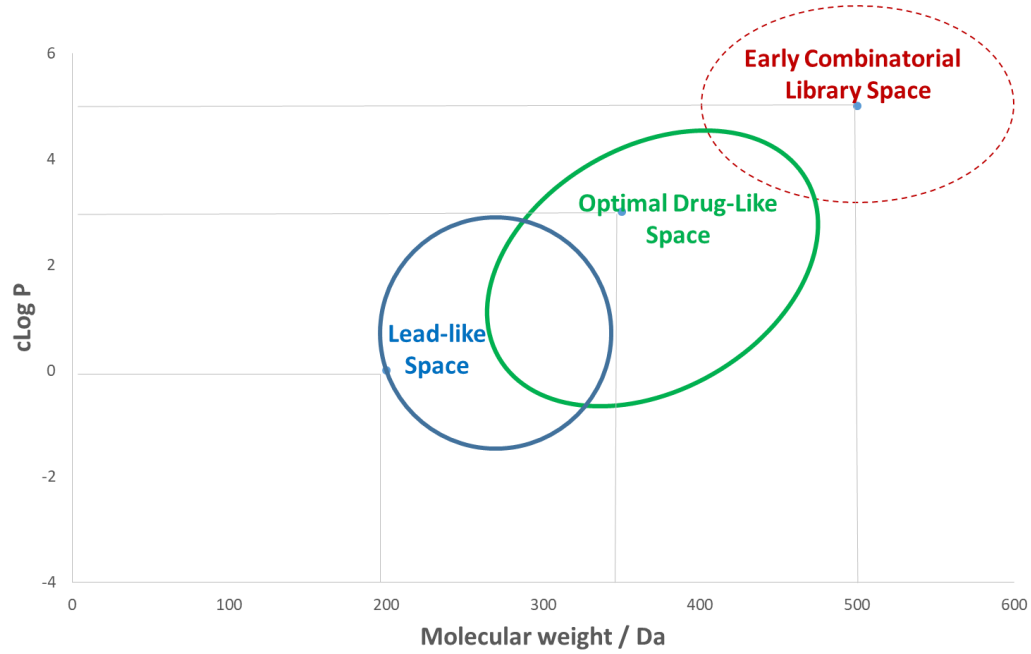
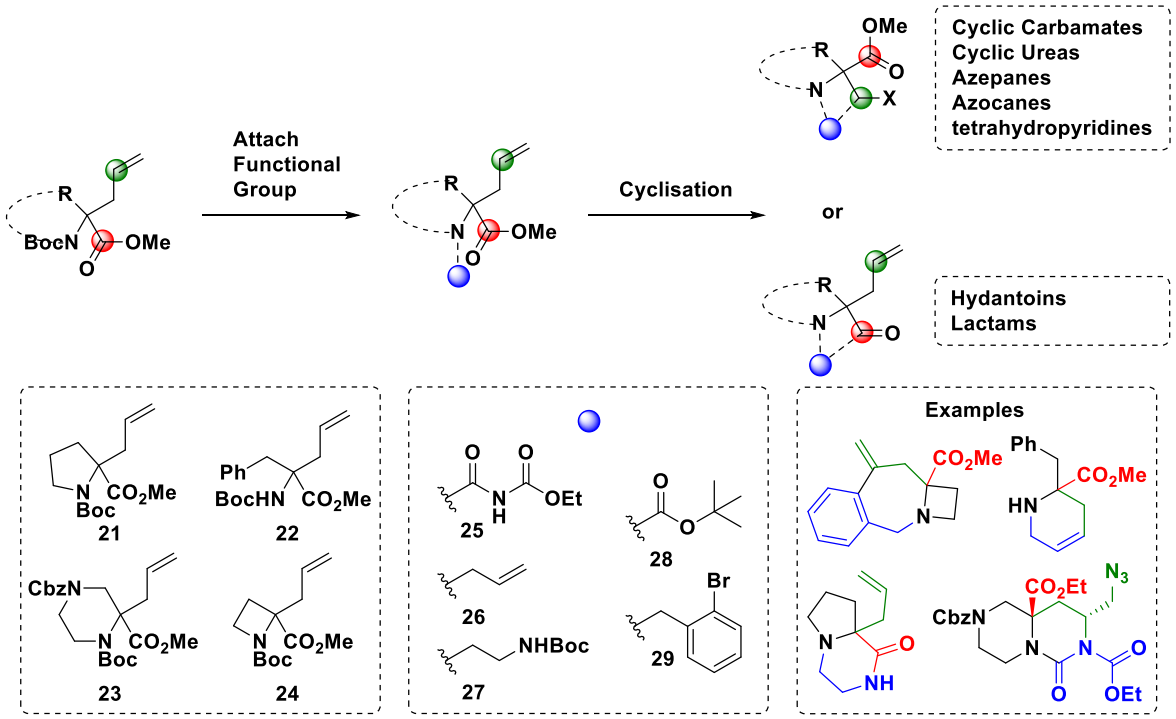


Figure 1.10: The optimal drug-like (green) and lead-like (blue) regions of chemical space can be defined in terms of lipophilicity (cLog P) and molecular weight. In general optimisation progresses through an increase in complexity causing increased molecular weight and increased lipophilicity, so the starting point should ideally have the scope for inflation of these properties, unlike early combinatorial space (red). Figure adapted from reference.[104]

In terms of practical library generation, lead-oriented synthesis aims to synthesise a diverse array of lead-like structures from inexpensive starting materials using robust and efficient chemical

transformations, such that follow up chemistry can be carried out rapidly. Furthermore, the chemistry used should be tolerant to a wide range of the polar functional groups that are attractive in drug discovery, whilst avoiding those functionalities with reactive centres that might prove counter-productive in lead optimisation. An example of this comes from Foley *et al.* in which four α-amino acid-derived building blocks were used with six reaction methodologies to generate a library of 22 lead-like scaffolds in 49 synthetic operations (Scheme 1.5).[106]



*Scheme 1.5: Synthesis of a lead-like library of 22 compounds from 4 α,α-disubstituted amino acids **21-24** using 6 reaction methodologies. For each α,α-disubstituted amino acid 5 different N-substituted compounds (acyl ureas **25**, allylamines **26**, 1,2-diamines **27**, Boc protected amines **28**, o-bromobenzylamines **29**) were prepared ready for cyclisation. Pairwise coupling of the nucleophilic allyl group with the nucleophilic N-acyl substituents (Boc and urea) upon activation with iodine and subsequent treatment with sodium azide gave cyclic carbamates and ureas. Pairwise coupling of the electrophilic carboxylate ester with nitrogen centred nucleophiles gave hydantoins (from the acyl urea) and lactams (from the amine). The aryl bromine could be exploited for a Heck cyclisation with the allyl group to give azepanes and azocanes, and finally a ring closing metathesis between the two allylic groups would furnish indolizidine alkaloid-like tetrahydropyridines. Figure adapted from reference.*[106]

1.5.2. Fragment-based Drug Discovery

A drug can be considered as a combination of multiple binding interactions which generate the required selectivity and potency. Fragment-based drug discovery (FBDD) is a technique that exploits this by using low molecular weight compounds to investigate these interactions separately and identify a

starting point or starting points for drug discovery.[107,108] There are two primary advantages to using FBDD over other drug discovery methods:

1) As the size of molecules decrease, the number of possible molecules also decreases exponentially, and therefore, using libraries of smaller molecules enables more efficient sampling of chemical space.[109]
2) Molecular complexity is an important concept in drug discovery; developed by Hann *et al.* it suggests that molecules with increased complexity have the potential to make more interactions with a protein target.[110] However, a molecule with multiple binding interactions can be rendered impotent by a single unfavourable binding interaction proving unfavourable to the overall binding.[111] Larger molecules have an increased risk of mismatch with the target protein site due to an unfavourable interaction,[112] FBDD aims to overcome this risk through the use of low molecular weight fragments. As a result of their small size, these bindings will be weak, however, they can provide the building blocks for a more complex series through combining and/or optimising fragments.[109] (Figure 1.11).

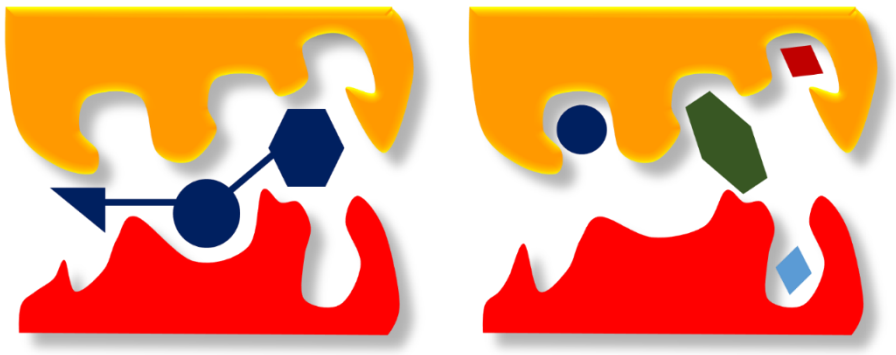


Figure 1.11: HTS hits often bind through multiple suboptimal interactions, whereas fragment hits involve fewer interactions, however the interactions present are of higher quality. Figure adapted from reference.[113]

A pharmacophore is defined as a single binding interaction between a ligand and a protein. Drugs generally consist of multiple connected pharmacophores and therefore the individual pharmacophores, as the simplest possible components of the drug, can be considered to represent its constituent fragments.[114] Within each pharmacophore, it is usually the polar interactions which drive binding, and therefore, fragments typically bind to "hot-spots" through these polar interactions within the ligand-binding site of the target.[115]

Once fragment hits have been identified, they can be optimised by linking, merging and growing into a high quality drug-like compound (Figure 1.12). However, chemical elaboration to grow the fragment can often be easier than merging and linking strategies.[107,109] It is this aspect with means that FBDD is especially useful for unprecedented target classes, because fragment optimisation can often use creative

and innovative pathways to evolve structurally simple starting materials into complex drug-like molecules, resulting in under-represented or completely novel scaffolds.[116]

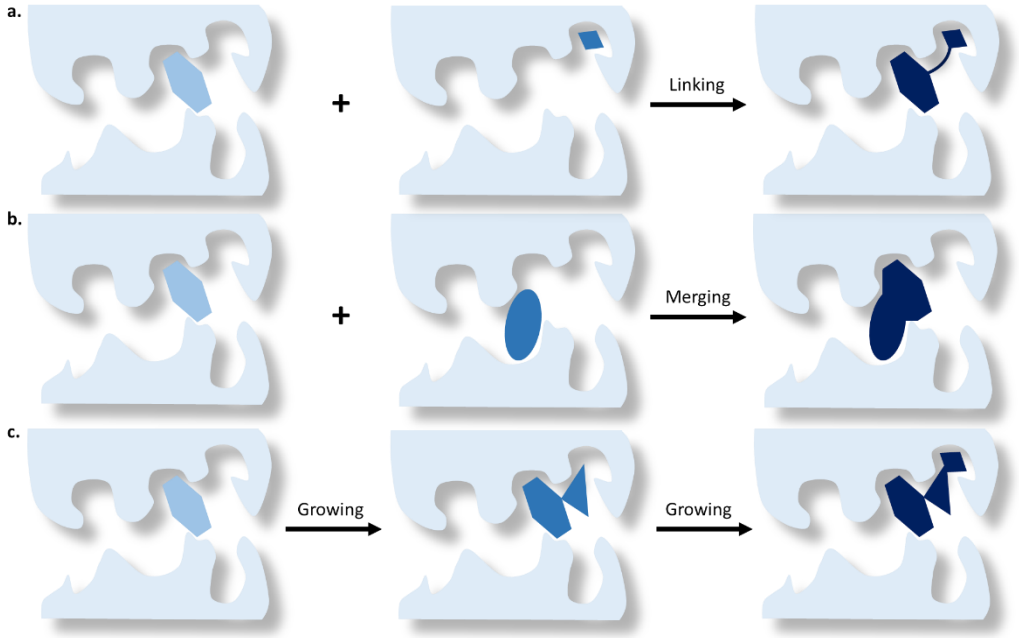


Figure 1.12: Three commonly used strategies for optimisation of fragment hits into lead like molecules. a. Linking aims to join two distinct fragment hits from adjacent pockets without disrupting their binding modes; b. merging aims to combine two distinct fragment hits found in overlapping binding sites; c. growing aims to chemically elaborate a single hit so as to pick up further ligand-protein interactions. These strategies are not orthogonal and can often be used in union for a FBDD program.

This approach to drug discovery has rapidly found success since its inception[117] as not only does it enable efficient sampling of chemical space and result in the evolution of novel scaffolds from simple starting points, but it also addresses some of the underlying problems that contribute to the high levels of attrition in drug discovery due to inflation of unfavourable compound properties.[101]

FBDD identifies low molecular weight hits that, although weak in potency, form high quality interactions with excellent binding energy relative to their small size and have the 'space' for optimisation into drug-like space. Therefore, the ideal fragment will have a high proportion of atoms directly involved in the binding interaction.[107,118] Ligand efficiency (LE) was therefore developed as a way comparing the binding efficiency of compounds of different sizes (Equation 1.1).[119,120]

Equation 1.1: Equation used to calculate ligand efficiency

$$Ligand\ Efficiency\ (LE) = \frac{Free\ Energy\ of\ Binding\ (1.4\ \cdot pIC_{50})}{Number\ of\ Heavy\ Atoms\ (HAC)}$$

A ligand efficiency of greater than 0.3 kcal per heavy atom implies that careful optimisation of the initial hit has the potential to yield a rule of 5 compliant 10 nM inhibitor.[118] Therefore an important aim in FBDD is to maintain a good ligand efficiency during the fragment optimisation process, such that

highly efficient drug-like molecules with desirable pharmacokinetic properties can be generated. In fact, where FBDD is concerned, this is often considered more important than potency alone.[120]

However, despite offering high ligand efficiency, the low molecular weights of fragments means that their binding affinity with the protein target will still be very weak, typically in the mM to 30 μM range[107] and as such, progress within FBDD has historically been limited by the sensitivity of available biophysical screening methods.[109,114] The development of both new and pre-existing biophysical techniques, including NMR screening,[109,121] mass spectrometry, surface plasma resonance (SPR) and X-ray crystallography,[109,122–124] has enabled the high-throughput screening of these weakly binding molecules.

Overall, FBDD is a highly intuitive drug discovery approach with the potential to generate highly potent and selective inhibitors, in particular for novel targets. FBDD is a relatively young drug discovery process, and as such due to the long approval process very few compounds thus far been marketed. However, there are over 30 FBDD-derived compounds in clinical development alongside two FDA approved drugs: Venclexta™ and Zelboraf® (Figure 1.13).[125]

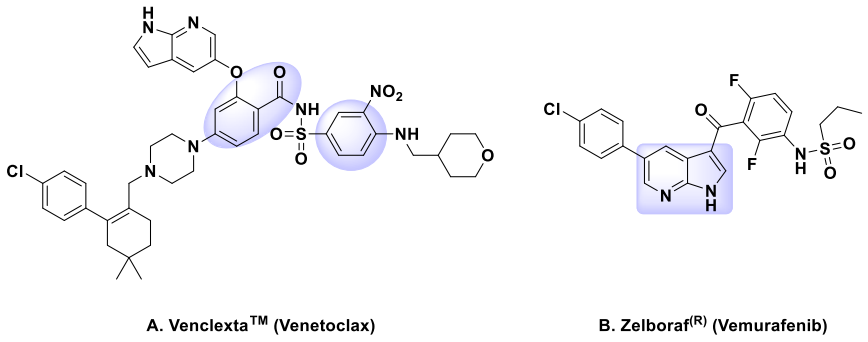


Figure 1.13: Two FDA approved drugs developed by the FBDD process, with the original fragment hits highlighted in pale blue. a. Venclexta™ was developed by Abbvie Inc. to treat chronic lymphocytic leukaemia (CLL) by blocking the anti-apoptotic B-cell lymphoma-2 (Bcl-2) protein, leading to programmed cell death of CLL cells. It was FDA approved in 2015; b. Zelboraf® was developed by Plexxikon and Genentech to treat late-stage melanoma via inhibition of the B-Raf kinase. It was FDA approved in 2011.

The development of Zelboraf® clearly illustrates the FBDD process (Figure 1.14).[126] Approximately 20,000 fragments were screened resulting in the idenitification of 238 compounds which demonstrated kinase inhibition across the three kinases screened, Pim-1, p38, and CSK. Co-crystallographic analysis of these fragments generated over 100 structures showing bound compounds. Of these, 7-azaindole demonstrated different binding modes across the four protein monomers in the asymmetric unit of Pim-1, suggesting a weak binding affinity. To improve the affinity, screening of a group of mono-substituted 7-azaindoles was carried out, and this identified the 3-aminophenyl analogue and mono-substituted azaindole, both which had single binding modes across the monomers but poor selectivity over other kinases. Subsequent screening and optimisation of more complex analogues led to the discovery of

PLX4720 and PLX4032, which both showed excellent selectivity and in-vitro inhibition of the mutant kinase, B-RafV600E. Pre-clinical trials demonstrated that PLX4032 potentially had better pharmacokinetic properties and this analogue was therefore promoted to clinical trials and eventually marketed as Zelboraf in 2011.[127]

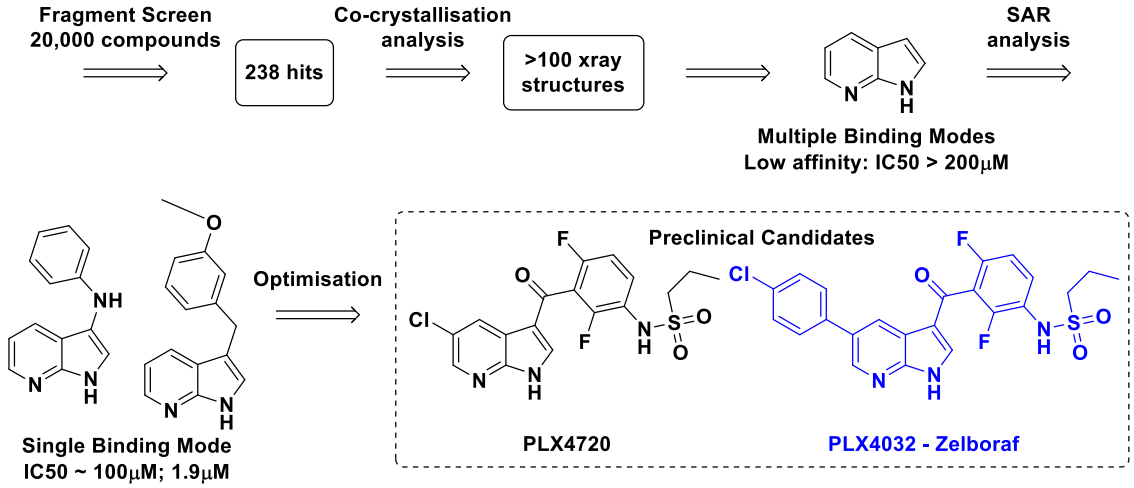


Figure 1.14: Development of Zelboraf® from an initial screening of approximately 20,000 compounds.

As with all the drug discovery processes described herein, success is generally determined by the quality of the screening library, and FBDD is no different.[128] As such a number of guidelines exist to aid the design of fragment libraries with diverse scaffolds and pharmacophores, for example the 'rule of 3' (Table 1.4):[116]

Table 1.4: Table describing the molecular properties and features used to describe fragments.[114]

Property	Guideline
Molecular recognition	Incorporation of functional groups for binding to the protein (these constitute the pharmacophore): these are usually polar groups.
Synthetic vectors	Incorporation of multiple synthetically accessible vectors for fragment growth in three-dimensions to access new binding interactions.
Physiochemical properties	Molecular size: $140 \leq MW \leq 230$ g mol^{-1}, $10 \leq HAC \leq 16$ heavy atoms; Lipophilicity: $0 \leq \text{clog } P \leq 2$ Screening properties: ≥ 5mM solubility in 5% DMSO, > 24h stability in solution Avoidance of functional groups known for high reactivity, aggregation in solution or false positives.
Synthetic tractability	Typically require 50-100 mg for screening Ideally ≤ 4 steps from commercially available starting materials
Shape	Variety of three-dimensional shapes for each scaffold and pharmacophore $0 \leq$ Freely rotatable bonds ≤ 3 $0 \leq$ Chiral centres ≤ 2

- Given the importance of scaffold diversity and since polar groups usually form the pharmacophore (ligand-protein binding interaction) it is necessary to incorporate multiple scaffolds for each binding pharmacophore. Therefore, when designing the synthetic routes for a fragment library, the most efficient approach is to choose conditions for each step that can tolerate the polar functionalities needed.
- Fragment elaboration aims to increase potency through the design and synthesis of compounds with the potential for new points of interaction, as identified from the x-ray crystal of the ligand-protein complex. Screening fragments with built-in functional handles streamlines the elaboration process, since it avoids the need to synthesise multiple new scaffolds to incorporate these handles and avoids the risk of changing the binding mode when these functional groups are incorporated further down the line.[129,130]
- Molecular complexity must be finely balanced within FBDD, as increased complexity can reduce the probability of achieving the optimal ligand-protein interactions, whereas decreased complexity risks missing interesting interactions and raising the levels of promiscuity.[130] In terms of three-dimensionality the same balancing act applies, with higher levels of three-dimensionality risking lower hit rates, but the more three-dimensional hits, although fewer in number, are generally found to have better ligand efficiency and synthetic tractability.[61] At the same time, final drug-like compounds with high levels of three-dimensionality can still be derived from completely flat initial fragment hits.[61,116]

FBDD projects are often inhibited by the lack of synthetic methodology available since the synthetic methodologies needed for fragment library synthesis need to be compatible with heteroatoms and polar groups, and generate structures with stereo- and regio-control.[114] By considering and developing robust methodology for fragment synthesis and elaboration, including elaboration in all three-dimensions (Figure 1.15), delays are avoided during the FBDD project without overly increasing the complexity of the fragments.[114]

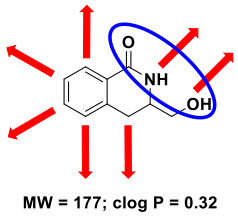


Figure 1.15: An example of an ideal fragment, with molecular weight and lipophilicity consist with the ranges specified, a polar functionality for protein binding (blue circle) and potential synthetically pre-planned growth vectors for fragment optimisation. Figure adapted from reference.[114]

2. Aims of the Project: Synthesis of Partially Saturated Heteroaromatic Scaffolds

Various screening paradigms have been, and continue to be, used in drug discovery, including those discussed: HTS, lead-oriented synthesis and FBDD. Within all of these paradigms, the success of screening endeavours is inherently dependent on the composition of the screening library employed. Going forwards, regardless of the paradigm being used, there needs to be greater consideration of the quality and composition of compound libraries, in particular ensuring that the libraries consist of diverse and biologically relevant molecules with appropriate physicochemcial properties. In addition, there needs to be an emphasis on the diversification of the libraries through the inclusion of more representative exemplars of singleton scaffolds.[42]

Overall, analysis of existing screening libraries, and even marketed drugs, has highlighted not only the lack of scaffold diversity but also the astoundingly small percentage of molecular scaffolds represented despite the vast size of chemical space. Hence there is a clear need for novel or atypical molecular scaffolds with increased levels of three dimensionality in small molecule screening libraries with the aim of accessing under-explored or novel biologically relevant chemical space and potentially yielding modulators of novel biological targets. In addition, the use of novel scaffolds is vitally important in the context of intellectual property considerations and patentability.

Ring systems are prevalent throughout biologically active chemical space, and within this sub-class nitrogen-containing heterocyclic ring systems represent scaffolds of particular utility, incorporating all the advantages of a ring system with the potential binding ability of heteroatoms into a single scaffold. Despite this, there is relatively little diversity in the nature of such scaffolds, with a particular lack of saturated systems and so novel sp^3-enriched nitrogen-containing heterocyclic ring systems represent targets of particular interest.

As highlighted, structural diversity within the library is extremely important for the success of screening endeavours. In this regard, it is important that the synthetic routes used to generate screening compounds be carefully designed such that multiple examples of the same scaffold can be easily accessed in order to address the prevalence of singular examples of scaffolds within current libraries.

Furthermore, the ease with which the screening compounds can be developed (in hit-to-lead and subsequent optimisation) is also a crucial consideration. Ideally, scaffold synthesis should be designed in such a way as to incorporate higher levels of three-dimensionality and polar functional groups in screening members from the outset, since these properties are considered highly attractive within drug discovery. In addition, chemical handles that are amenable to elaboration in all three-dimensions

throughout the structure should be considered in these initial designs, so as to avoid the need to develop new methodology or remake the scaffold *via* an alternative route.

Based on these considerations, partially saturated heterocyclic scaffolds of the general form **30** were identified as being of potential value and broad utility within drug discovery (Figure 2.1). It was envisaged these scaffolds could be synthesised in such a way as to be applicable to fragment-like, lead-like or drug-like space dependent upon the size and properties of the compounds generated. As such, the particular focus of this work is to demonstrate the possibility of developing highly modular and efficient routes towards these types of molecules, such that multiple related scaffolds can be generated.

Specifically, the targets would feature a bicycle consisting of an aromatic heterocycle fused to a partially saturated heterocycle, with variation in both the aromatic heterocycle and the size of the partially saturated heterocycle.

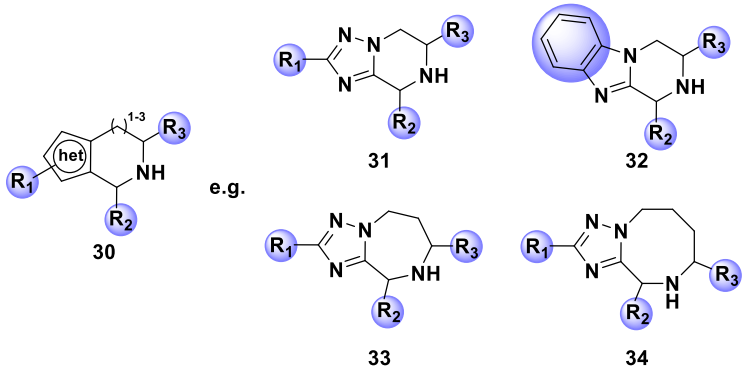


*Figure 2.1: General structure of the desired partially-saturated heterocyclic scaffold 30 and examples of some potential targets **31-34**.*

These partially saturated heteroaromatic scaffolds were chosen for a number of reasons:

1) It was expected that the core scaffold would incorporate the advantages of both aromatic and saturated heterocyclic scaffolds. The sp^3-enriched ring would increase the three-dimensional character relative to the majority of compounds in existing libraries, and the consequent increase in complexity should improve the potential selectivity and potency without decreasing the potential hit rate;
2) Compounds featuring these types of partially saturated heteroaromatic scaffolds have been identified as having biological activity against a range of targets (Figure 2.2), and so a series of related fragments should not only demonstrate novel biological activity if developed into a screening collection, but will also increase library diversity by reducing the number of singular exemplars of these scaffolds;
3) These scaffolds can form the basis of a diverse collection of compounds, through variation in the identity of the heteroaromatic, the size of the partially saturated heterocycle and the regio- and stereochemical arrangement of functional groups around the scaffold.

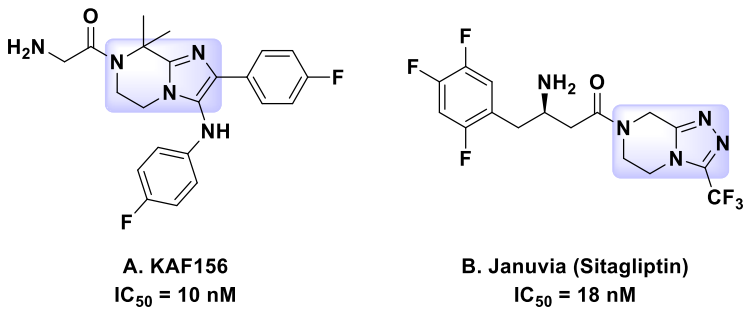
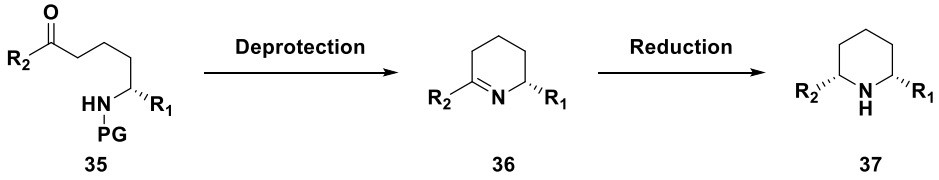


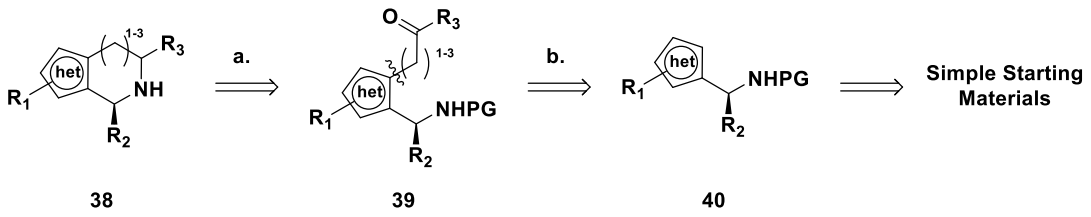
Figure 2.2: Two examples of bioactive compounds containing functionalised partially-saturated scaffolds (highlighted in pale blue): A. KAF156, a potent compound with activity against the Plasmodium falciparum and Plasmodium vivax forms of the malaria parasite. Developed by Novartis, it finished Phase II clinical trials in 2017.[131,132] *B. Januvia is a potent inhibitor of dipeptidyl peptidase IV which is implicated in the treatment of hyperglycaemia for patients with type II diabetes. Developed by Merck & co. it has been FDA approved since 2006.*[133–135]

Partially saturated heterocyclic scaffolds have previously been synthesised a number of ways, including selective hydrogenation of bicyclic heteroaromatics[136,137] and *via* catalytic, asymmetric intramolecular aza-Friedel-Crafts reactions.[138] In all these cases, there is limited regio- and stereo-control of the substitution pattern in the partially saturated ring, restricting their utility in library synthesis. Previous examples to access non-fused piperidine rings diastereoselectively used deprotection of the amine enabling generation of the imine **36** followed by reductive amination to amine **37** (Scheme 2.1).[139–143]



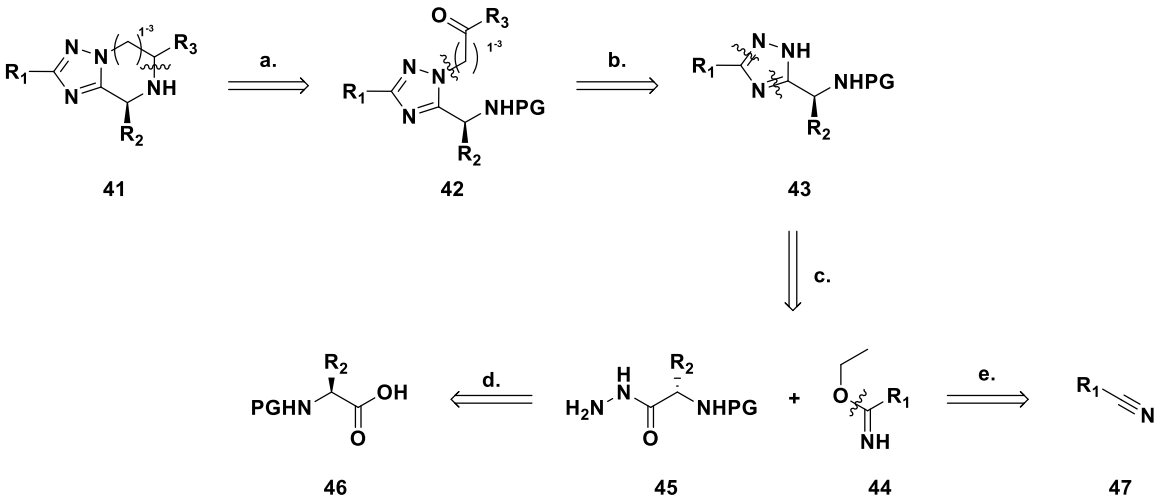
Scheme 2.1: Common route towards accessing diastereoselective piperidine rings. PG = Protecting Group

This work proposed to harness this diastereoselective approach to the formation of a cyclic secondary amine, but within fused bicyclic system **38**. Towards this end, it was anticipated that the final reductive amination and deprotection could be carried out on ketone **39**, which in turn could be formed by alkylation of the corresponding heterocycle **40** (Scheme 2.2). It was hoped that all the desired heterocycles could be generated in minimal numbers of steps from simple starting materials, thus incorporating the key principles of DOS. The diversity of the library could be generated through variation of the heteroaromatic, the size of the partially saturated heterocycle and the nature and spatial arrangement of the functional groups $R_{1\text{-}3}$. Furthermore, depending upon the size and nature of the R groups chosen, the library synthesised could comprise fragment-like, lead-like or drug-like molecules.



Scheme 2.2: General Retrosynthetic analysis of the partially saturated heterocyclic scaffolds.PG = protecting group

To this end, the triazole-based partially saturated heteroaromatic scaffold **41** was targeted first, to demonstrate the robustness of the methodology, before applying it to other novel scaffolds. It was envisaged that reductive amination and deprotection would yield the desired bicyclic scaffold **41** from ketone **42**. This is turn could be formed by alkylation of the triazole ring **43**. It was proposed that cyclisation of an imidate **44** and an amino hydrazide **45** would form the triazole itself, with the amino hydrazide **45** coming from the corresponding amino acid **46** and the imidate derived from the corresponding nitrile **47**: both inexpensive, simple and commercially available materials.



Scheme 2.3: Retrosynthetic analysis of the partially saturated heterocyclic scaffold based around triazole: a. One-pot deprotection and reductive amination; b. nitrogen alkylation; c. triazole cyclisation; d. conversion of acid to hydrazide via ester; e. formation of imidate.

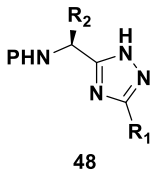
With a retrosynthesis in place, studies towards the triazole-based partially saturated heteroaromatic scaffolds commenced.

3. Results and Discussion

3.1. Studies towards Achieving Diastereoselctive Scaffolds

3.1.1. Initial Studies with the Triazole-Based Scaffold

The partially saturated triazole-based scaffold **41** was selected as the first target scaffold, on which to test the proposed synthetic route. In line with the retrosynthetic analysis detailed in Scheme 2.1, the first challenge was the construction of 3,5-bisubstituted 1,2,4-triazole scaffold **48** (Figure 3.1).

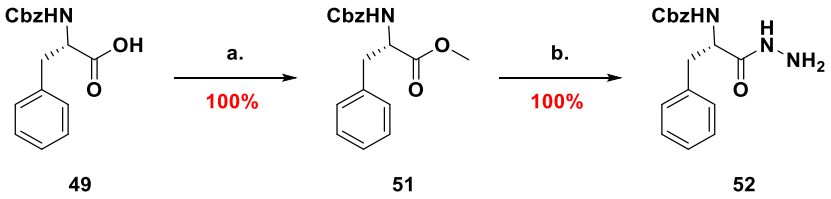


48

Figure 3.1: 3,5-bisubstituted 1,2,4-triazole scaffold 1, P = Protecting Group

A literature search revealed significant precedent for the construction of this type of scaffold.[144,145,154–161,146–153] The most commonly reported synthetic route towards the synthesis of these substrates was the reaction between an amino hydrazide derivative of an amino acid and an imidate. This was particularly appealing since it took advantage of the large chiral pool provided by both natural and unnatural amino acids. When considering the protecting group, examples of both *tert*-butoxycarbonyl (Boc) and carboxybenzyl (Cbz) groups were reported. Given the intended route, it was essential to use a base-stable functionality, as well as a functionality with a deprotection method which would be compatible with both imine formation and reduction. As such, the carboxybenzyl (Cbz) group was chosen due to its well-known stability and possible removal *via* a variety of suitable methods.[162]

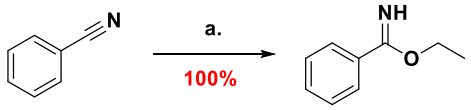
For the initial studies, Cbz-*L*-phenylalanine **49** and benzonitrile **50** were chosen as the initial starting materials, due to the lack of reactivity of the phenyl and benzyl groups corresponding to R_1 and R_2 respectively. The amino hydrazide derivative of Cbz-*L*-phenylalanine was constructed in two steps from **49**. First successful conversion to the amino ester **51** was carried out in excellent yield using excess thionyl chloride in methanol,[163] followed by nucleophilic substitution of the ester using excess hydrazine monohydrate to yield **52**, again in excellent yield (Scheme 3.1).[164]



49 51 52

*Scheme 3.1: Synthesis of benzyl (S)-(1-hydrazinyl-1-oxo-3-phenylpropan-2-yl)carbamate, **52**, from the corresponding Cbz-L-phenylalanine amino acid: a. Cbz-L-phenylalanine **49** (1.0 eq.), $SOCl_2$ (1.4 eq.), CH_3OH, 3h, rt, 100% **51**; b. **51** (1.0 eq.), $NH_2NH_2{\cdot}H_2O$ (5.0 eq.), CH_3OH, 12h, rt, 100%, **52**.*

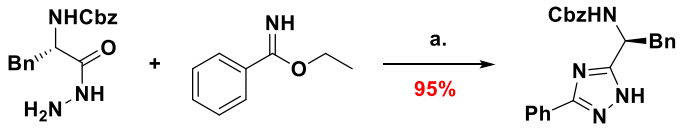
Simultaneously, the efficient transformation of benzonitrile **50** into the corresponding imidate **53** was carried out quantitatively using acetyl chloride and ethanol (Scheme 3.2).[165]



50 53

*Scheme 3.2: Synthesis of ethylphenylcarbimidate, **53**, from the corresponding benzonitrile: a. Benzonitrile **50** (1.0 eq.), AcCl (8.0 eq.), EtOH (12.0 eq.), 12h, 0 °C to rt, 100% **53**.*

With these two components in hand, the literature procedure for the synthesis of the 3,5-disubstituted triazole scaffold **54** was carried out. This entailed refluxing the two components, first in ethanol, then acetic acid.[148] Of particular note is that all of these preliminary reactions could be carried out with consistently high yields on multi-gram scales (Scheme 3.3).

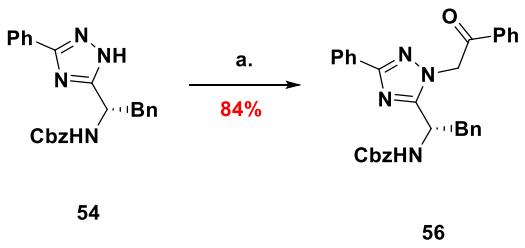


52 53 54

*Scheme 3.3: Synthesis of benzyl (S)-(2-phenyl-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate, **54**, from the corresponding amino hydrazide and imidate: a. i. **52** (1.0 eq.), **53** (1.2 eq.), EtOH, 6h, reflux; ii. AcOH, 2h, reflux, 95% **54**.*

For the alkylation of triazole **54** a nucleophilic substitution using an α-bromoketone was envisaged. Whilst there are relatively few examples of triazole alkylations using this particular type of electrophile, there is a reasonable amount of literature precedent for alkylation in general.[166–171] Potassium carbonate was by far the most prevalent base used for this type of reaction,[166,167,169–171] and therefore was chosen as the starting point. Dimethyl formamide (DMF)[170,171] and acetone[166,169] are both commonly used solvents for alkylations; due to the improved solubility of both the product and base in DMF this was

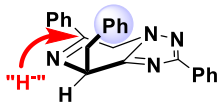
chosen initially, and combined with 2-bromoacetophenone **55** gave an 80% yield. Unfortunately, the DMF proved difficult to remove and therefore a switch to acetone was trialled. Pleasingly, this proved equally suitable and an 84% yield was achieved (Scheme 3.4).



54 **56**

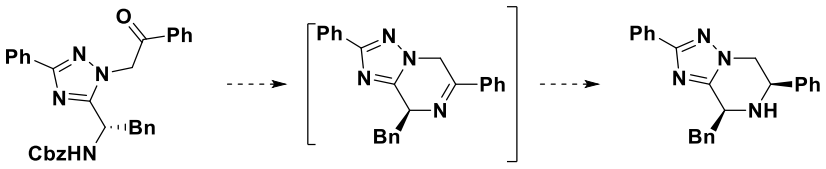
*Scheme 3.4: Synthesis of benzyl ((1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)methyl)carbamate, **55**, from the corresponding triazole: a. **54** (1.0 eq.), 2-bromoacetophenone **55** (1.2 eq.) K_2CO_3 (1.0 eq.), acetone, 12h, rt, 84% **56**.*

With gram-scale quantities of **56** in hand, a number of routes towards achieving the cyclised amine were explored. It was hoped that this could be achieved in a single pot, with deprotection of the carboxybenzyl group enabling spontaneous cyclisation of the primary amine with the ketone, to form imine **57**. Addition of a reductant would then enable reduction of imine **57** to amine **58**, with a *syn*-relationship between the phenyl and benzyl groups, as a result of the reduction being driven by the steric bulk of the benzyl group alpha to the imine (Figure 3.2, Scheme 3.5).



57

Figure 3.2: Figure illustrating the three-dimensional shape of the imine such that the steric bulk of the benzyl group will drive the syn-diastereoselectivity of the reduction.

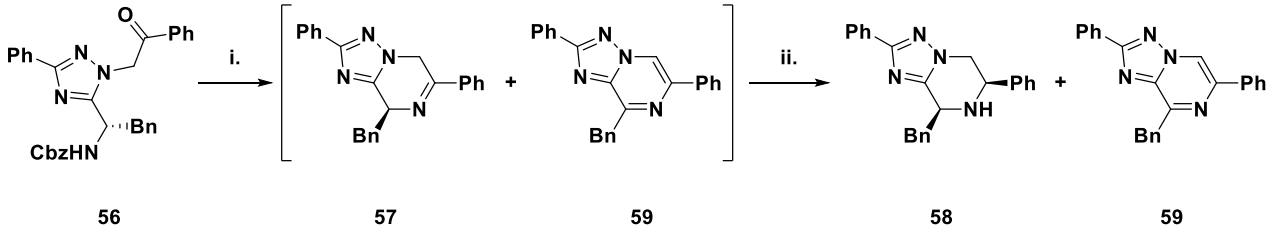


56 **57** **58**

Scheme 3.5: Proposed route to piperazine ring formation

Carboxybenzyl deprotection is most commonly carried out either by catalytic hydrogenation or with a strong Brønsted or Lewis acid.[162,172,173] Initially the use of acids was explored for the deprotection (Table 3.1).

Table 3.1: Testing acidic conditions for the deprotection and following reductive amination.



56 **57** **59** **58** **59**

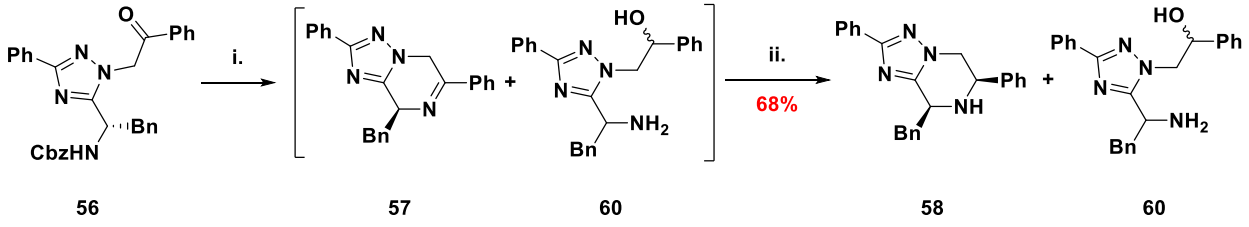
Entry		Conditions	Yield 58 (%)
1	i.	HBr (33 wt % in AcOH), 15 mins, rt	41
	ii.	$NaBH_4$, THF, 1h, rt	
2	i.	HBr (33 wt % in AcOH), 15 mins, rt	69
	ii.	$LiBH_4$, Et_2O, 1h, rt	
3	i.	HBr (33 wt % in AcOH), 15 mins, rt	66
	ii.	$NaCNBH_3$, CH_3OH, 1h, rt	
4	i.	HBr (33 wt % in AcOH), CH_2Cl_2, 30 mins, rt	65
	ii.	$NaCNBH_3$, CH_3OH, AcOH, 1h, rt	
5	i.	TFA, CH_2Cl_2, 12h, rt	0
	ii.	$NaCNBH_3$, CH_3OH, 1h, rt	
6	i.	BBr_3, CH_2Cl_2, 15 mins, rt	63
	ii.	$NaCNBH_3$, CH_3OH, AcOH, 1h, rt	
7	i.	BCl_3, CH_2Cl_2, 30 mins, rt	87[a]
	ii.	$NaCNBH_3$, CH_3OH, 1h, rt	
8		$BF_3 \cdot OEt_2$, Ph_3SiH, CH_2Cl_2, 30 mins, -78 °C then 2h, rt	0

a. This yield was not reproducible due to aromatisation issues.

The use of hydrogen bromide in acetic acid, to remove the carboxybenzyl protecting group, has good precedent in the literature, and it was hoped that, if needed, the acid would catalyse the imine formation.[174–177] The reactions were followed *via* LCMS, and this demonstrated successful deprotection and cyclisation to the imine **57**, however there was evidence of some aromatisation of the six-membered ring **59**. Nevertheless, the reduction step was tested, using sodium borohydride[178,179] (Table 3.1, Entry 1), lithium borohydride[180] (Table 3.1, Entry 2) and the milder sodium cyanoborohydride[181,182] (Table 3.1, Entry 3), with the hope that the latter, milder reagent would be sufficient, so that it could be used as the standard reducing agent in all subsequent reductions. It was pleasing to note that this was the case, these three reactions giving 41%, 69% and 66% of the desired scaffold **58** respectively. With this range of yields a result of the aromatisation to **59**, from the first step.

In the hope of minimising aromatisation, a single equivalent of hydrogen bromide in dichloromethane was used (Table 3.1, Entry 4), diluting the deprotection and cyclisation step,[183,184] however a similar, yield of 65% was achieved, again as a result of the aromatisation. In order to circumvent this, other acids were tested for the deprotection: trifluoroacetic acid (TFA)[185] (Table 3.1, Entry 5), boron tribromide[186,187] (Table 3.1, Entry 6) and boron trichloride[188,189] (Table 3.1, Entry 7). Of these, the trifluoroacetic acid, was not sufficient to remove the protecting group, and starting material **56** remained after 12 hours; boron tribromide encountered the same problems as the hydrogen bromide, resulting in a moderate 63% yield with the remaining material aromatised; the milder boron trichloride was more successful, achieving an excellent 87%, with a small amount of the aromatic product **59** observed. Despite this promising yield, upon repetition, this reaction gave quite variable yields as a result of the aromatisation. Finally, boron trifluoride combined with triphenylsilane was tested (Table 3.1, Entry 8), in which it was hoped that the deprotection and reduction would take place without the need to add the reductant in a second step, and as a result the imine would be reduced upon formation, minimising the probability of aromatisation; however after 12 hours, only starting material remained.

A paper from Sultane *et al.* suggested that the use of trimethylsilyl trifluoromethane sulfonate should enable imine formation without the deprotection, the triethylsilane then reducing the generated *N*-acyl iminium ion intermediate *in-situ* (Scheme 3.6).[190] Monitoring *via* LCMS instead demonstrated the deprotection and imine formation alongside a small amount of reduction of the ketone before imine formation could take place, thus generating alcohol **60**. After 24 hours with no evidence of *in situ* imine reduction, sodium cyanoborohydride was added to generate **58** in a moderate yield, as a result of the earlier ketone reduction circumventing imine formation.



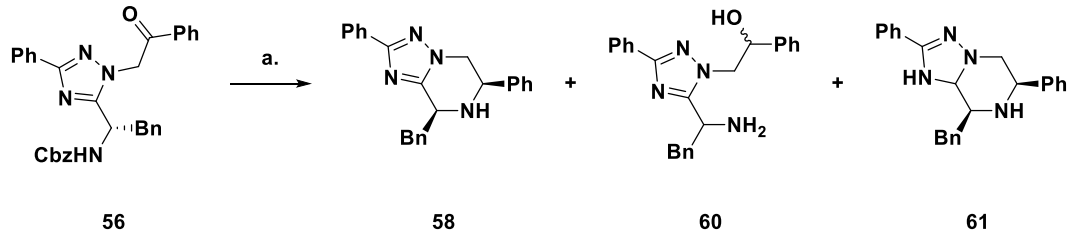
Scheme 3.6: Synthesis of (6R,8S)-8-benzyl-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine ***58:*** *i.* ***56*** *(1.0 eq.), TMSOTf (1.2 eq.), Et_3SiH (1.2 eq.), CH_2Cl_2, 12h, -78 °C; ii. $NaCNBH_3$ (1.2 eq.), CH_3OH, 3h, rt, 68%* ***58****.*

With the problems encountered using acidic conditions for the deprotection, catalytic hydrogenation was tested, in the hope that under reductive conditions the oxidation of the piperazine ring would not be observed and that the conditions could be tempered such that the heterocycle would be stable (Table 3.2).

Hydrogen and catalytic palladium on carbon are commonly used for the deprotection,[191,192] however, for this substrate no evidence of desired scaffold **58** was found; instead, reduction of the ketone was observed, alongside carboxybenzyl reduction such that both diastereomers of compound **60** were generated (Table 3.2, Entry 1). This suggested that the ketone reduction was happening at a faster rate than imine formation once the primary amine had been unveiled. In addition, there was some evidence of reduction of the triazole ring to give **61**. Exploring the literature conditions for this step suggested that a switch to ethyl acetate as the solvent would favour imine formation under reductive conditions,[193] however, no reaction was observed under these conditions (Table 3.2, Entry 2).

Finally, palladium dihydroxide on carbon was tested due to its prevalent use for the removal of carboxybenzyl protecting groups.[162,172,173] Under these conditions, no reduction of the triazole ring was observed, even after 24 hours, however, LCMS analysis of the crude reaction mixture revealed significant formation of diastereomers **60**, as a result of the rapid ketone reduction as observed with palladium on carbon (Table 3.2, Entry 3). As a result, only a 41% yield of **58** was achieved.

Table 3.2: Testing of catalytic hydrogenation for carboxybenzyl removal and reductive amination.



56 **58** **60** **61**

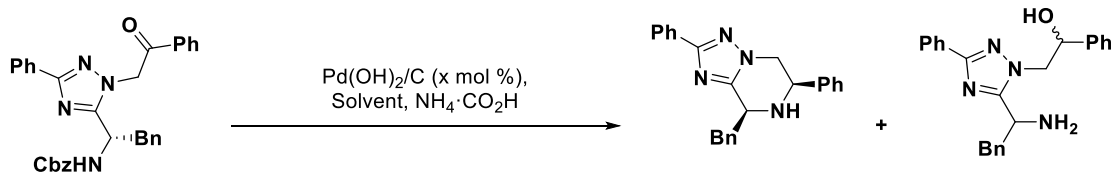
Entry	Conditions	Yield 58 (%)
1	a. H_2, Pd/C, CH_3OH,12h, rt	0
2	a. H_2, Pd/C, EtOAc, 12h, rt	0
3	a. H_2, $Pd(OH)_2$/C, CH_3OH, 24h, rt	41

Given that reduction of the triazole was not apparent under these conditions, it was hoped that optimisation could supress the undesired ketone reduction (Table 3.3).

For practical reasons, this optimisation process was carried out using ammonium formate as the hydrogen source.[162,172,194] In an attempt to promote imine formation at a faster rate than ketone reduction 2 equivalents of triethylamine were added, and this saw some improvement (Table 3.3, Entry 1); an increase to 15 equivalents further improved the ratio of products, although not to synthetically useful levels (Table 3.3, Entry 2). Following this, a range of solvents and bases were tested. Disappointingly, these all either returned the original triazole **54**, starting material **56** or gave a poor ratio of products

(Table 3.3, Entries 3 - 12). There was some literature precedent for the addition of water,[195] and, upon testing, this gave the best ratio (Table 3.3, Entry 14).

Table 3.3: Optimisation of conditions for the reductive deprotection and amination.

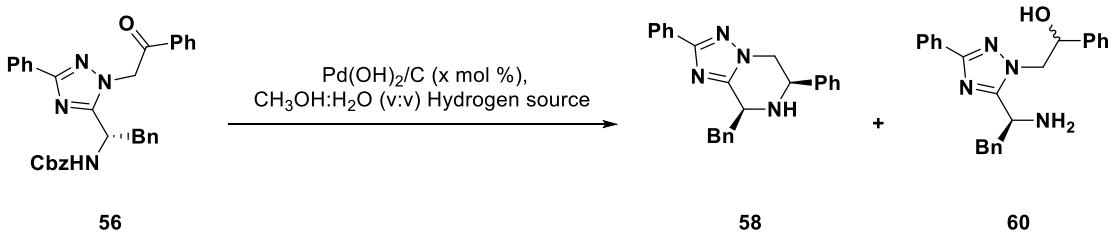


56 **58** **60**

Entry	x	Solvent	Additives (eq.)	Ratio 58:60	Side Products
1	5	^{i}PrOH	NEt_3 (2)	1:0.94	n/a
2	1	CH_3OH	NEt_3 (15)	1:0.61	n/a
3	5	CH_3OH	K_2CO_3 (15)	n/a	**54**
4	5	CH_3OH	Pyridine (15)	n/a	**56**
5	5	CH_3OH	NaOAc (15)	n/a	**54**
6	5	CH_3OH	Pyrrolidine (15)	n/a	**56**
7	5	EtOAc	K_2CO_3 (15)	n/a	**56**
8	5	EtOAc	Pyridine (15)	n/a	**56**
9	5	EtOAc	NEt_3 (15)	n/a	**56**
10	5	Toluene	K_2CO_3 (15)	1:0.67	n/a
11	5	Toluene	Pyridine (15)	1:0.08	n/a
12	5	Toluene	NEt_3 (15)	1:0.67	n/a
13	5	CH_3OH:H_2O (1:1 v/v)	None	1:0.07	n/a

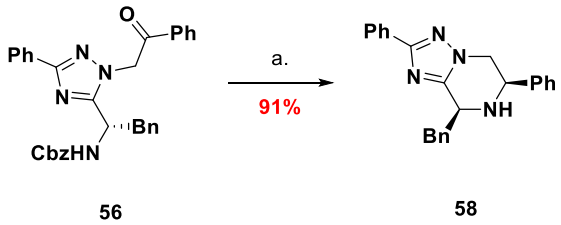
With the identification of water as the additive required to supress the undesired reduction of the ketone, it was then necessary to optimise the conditions further. This was done by finely tuning the other variables, such as the equivalents of catalyst used, the ratio of methanol and water and the hydrogen source used (Table 3.4). From this optimisation process it was found that below 3:1 CH_3OH:H_2O, the reaction was significantly slower, with entry 4 showing a mixture of starting material **56** and product **58** after 48h**.** Thus the optimal conditions were found (Table 3.4, Entry 3; Scheme 3.7).

Table 3.4: Further optimisation of conditions.



56 **58** **60**

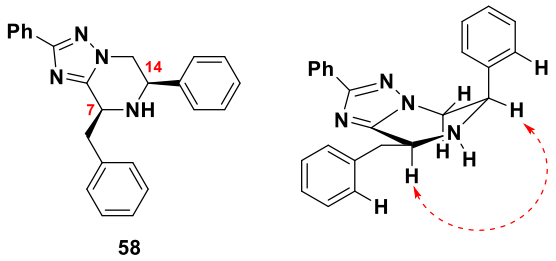
Entry	x	$CH_3OH:H_2O$ (v:v)	Hydrogen Source	Ratio 58:60	Side Products
1	10	3:1	$CO_2H{\cdot}NH_4$	1:0.07	n/a
2	10	3:1	H_2	1:0.49	n/a
3	20	3:1	$CO_2H{\cdot}NH_4$	1:0.06	n/a
4	20	2:1	$CO_2H{\cdot}NH_4$	n/a	**56**
5	20	1:3	$CO_2H{\cdot}NH_4$	n/a	**56**
6	20	0:1	$CO_2H{\cdot}NH_4$	n/a	**56**



56 **58**

*Scheme 3.7: Synthesis of (6R, 8S)-8-benzyl-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine, **58**, using the optimised reductive deprotection and amination conditions: a. **56** (1.0 eq.), $NH_4{\cdot}CO_2H$ (30 eq.), $Pd(OH_2)/C$ (20 mol%), $CH_3OH:H_2O$ (3:1 v/v), 12h, rt, 91%, >20:1 d.r. **58**.*

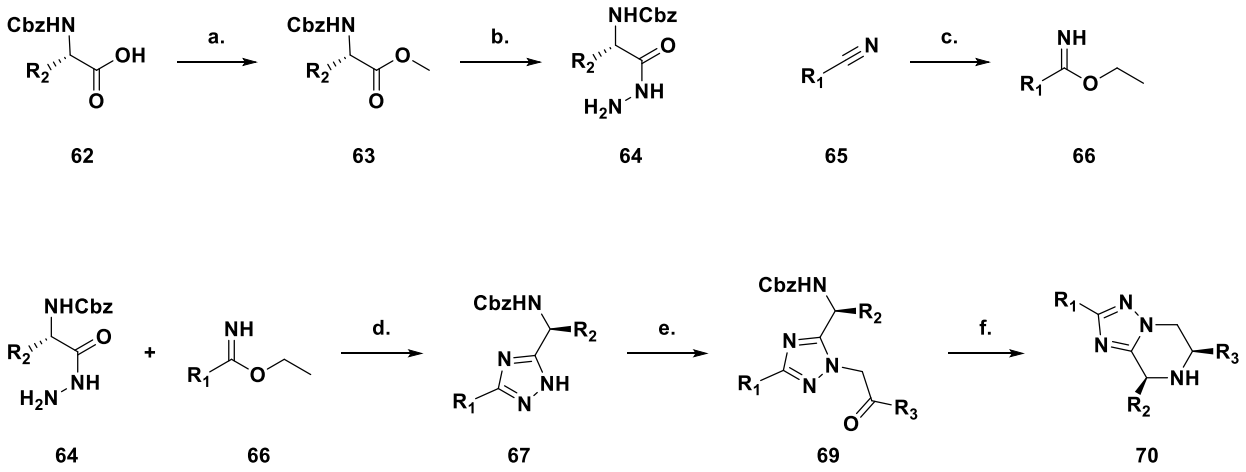
Key NOE interactions were identified to support the relative stereochemistry in compound **58**; in particular, correlation of protons 7 and 14 provided evidence of their *cis*-relationship (Figure 3.3).



58

Figure 3.3: Figure highlighting key selected NOE interactions supporting the relative stereochemistry

Following these results, it was established that the best route from **62** and **65** to **70** was *via* the following route (Scheme 3.8).



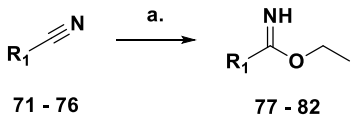
*Scheme 3.8: Summary of the planned route for the synthesis of triazole-based scaffolds: a. Cbz-L-amino acid **62** (1.0 eq.), $SOCl_2$ (1.4 eq.), CH_3OH, 3h, rt; b. **63** (1.0 eq.), $NH_2NH_2{\cdot}H_2O$ (5 eq.), CH_3OH, 12h, rt; c. nitrile **65** (1.0 eq.), AcCl (8.0 eq.), EtOH (12.0 eq.), 12h, 0 °C to rt; d. i. **64** (1.0 eq.), **66** (1.2 eq.), EtOH, 6h, reflux, ii. AcOH, 2h, reflux; e. **67** (1.0 eq.), α-bromoketone **68** (1.2 eq.) K_2CO_3 (1.0 eq.), acetone, 12h, rt; f. **69** (1.0 eq.), $NH_4{\cdot}CO_2H$ (30 eq.), $Pd(OH_2)/C$ (20 mol%), CH_3OH:H_2O (3:1 v/v), 12h, rt.*

3.1.2. Scope of the Route

With this in hand, it was necessary to demonstrate the applicability of this route to a range of functional groups. Both alkyl groups, to increase the molecular complexity and three-dimensionality, and aryl groups, that might be able to form π-π interactions with protein targets, were introduced. Additionally, polar groups that might be able to form hydrogen-bonding interactions with protein targets and increase the aqueous solubility.

To this end, the first step was the construction of the imidate and amino hydrazide building blocks. The imidates, imidates **77** to **82**, were synthesised as previously from the corresponding nitriles, **71** to **76** (Table 3.5) in excellent yields. When considering the groups included in the R_1 position, 5-hexene was chosen to illustrate the accessibility of alkyl chains, which are often incorporated to fill hydrophobic pockets. Although it was anticipated that alkene and alkyne groups would be reduced in the reductive deprotection and amination[196] (Table 3.5, Entry 1), this functionality had been included from the outset in the anticipation that the deprotection step could be done under acidic conditions such that these groups could be tolerated. Cyclopropyl was included for two reasons: firstly to illustrate the compatibility with alkyl rings, and secondly since the cyclopropyl group is frequently identified in successful drugs (Table 3.5, Entry 2).[197] The following three imidates included bear *para*-substituted aryl groups: trifluoromethyl is a common moiety within drug discovery,[198,199] and in addition functions as an electron withdrawing example; on the other end of the scale, methoxy would provide the electron donating example, and if the methyl group were removed would provide an additional exit vector for adaptation; bromine is incorporated as it provides an exit vector for late-stage functionalisation (Table 3.5, Entries 3-5). The same justifications lay behind the choice of the 2-*p*-bromobenzyl group, however, the additional flexibility provided by this methylene linker would allow the substrate to assume more conformations, thus improving the probability of it being accommodated into the pockets of potential protein targets (Table 3.5, Entry 6). The bromine-containing substituents were expected to be problematic in the final reductive amination step, since the palladium dihydroxide conditions used are similarly used for dehalogenation (Table 3.5, Entries 4 & 6).[200] It was hoped that the deprotection and subsequent reductive amination might proceed faster than the dehalogenation, such that careful monitoring might provide access to the bromine substituted scaffolds.

*Table 3.5: Synthesis of imidates **77** – **82** with of a range of functional groups in the R_1 position: a. Nitriles **71 - 76** (1.0 eq.), AcCl (8.0 eq.), EtOH (12.0 eq.), 12h, 0 °C to rt.*

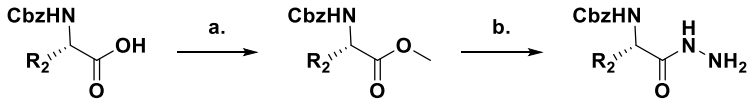


71 - 76 77 - 82

Entry	Starting Material	R_1	Compound	Yield X (%)
1	**71**	$(CH_2)_3CHCH_2$	**77**	100
2	**72**	Cyclopropyl	**78**	69
3	**73**	*p*-PhCF_3	**79**	80
4	**74**	*p*-PhBr	**80**	66
5	**75**	*p*-PhOMe	**81**	89
6	**76**	CH_2-*p*-PhBr	**82**	92

Concurrently, the amino hydrazide building blocks were constructed from the analogous carboxybenzyl protected amino acids **83** to **88**. First, the amino esters **89** to **94** were synthesised, in excellent yields, and all on a gram-scale (Table 3.6). From these, excess hydrazine monohydrate in methanol generated the desired amino hydrazides **95** to **100** in excellent yields. To showcase the potential of this route to generate a vast array of substrates, incorporating a variety of functional groups, careful thought was given into the selection of substituents at the R_2 position. Serine, with its primary alcohol, would provide an excellent handle for late-stage modifications, such as esterifications, substitutions and oxidations (Table 3.6, Entry 1). Valine would provide proof of concept of a branched alkyl group suitable for filling small hydrophobic pockets (Table 3.6, Entry 2), whilst tryptophan would illustrate the compatibility of the methodology with non-integral nitrogen-based heterocycles, whilst simultaneously providing a second handle for functionalisation (Table 3.6, Entry 3). Tyrosine would illustrate the applicability of aryl groups and, as with serine, provide another alcohol-based exit vector (Table 3.6, Entry 4). Proline provided a particularly interesting example, since the final scaffold generated would be 5,6,5-tricyclic scaffold, bearing two saturated rings (Table 3.6, Entry 5). Finally, methionine would exemplify the possibility of including sulphur-based functional groups (Table 3.6, Entry 6). Although sulphur is a known poison for palladium-based catalysts,[201–203] it was hoped that the use of stoichiometric palladium might be sufficient to overcome this.

*Table 3.6: Synthesis of amino hydrazides **95 - 100** with a range of functional groups in the R_2 position: a. Cbz-L-Amino acids **83 - 88** (1.0 eq.), $SOCl_2$ (1.4 eq.), CH_3OH, 3h, rt; b. **89 - 94** (1.0 eq.), $NH_2NH_2 \cdot H_2O$ (5.0 eq.), CH_3OH, 12h, rt.*

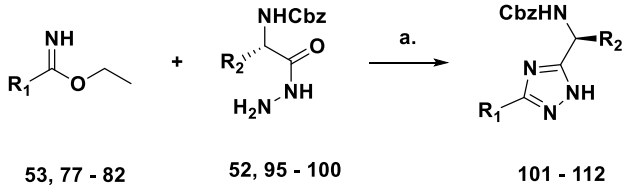


83 - 88 **89 - 94** **95 - 100**

Entry	Starting Material	Amino Acid	R_2	Yield Amino Ester (%)		Yield Amino Hydrazide (%)	
1	**83**	Serine	CH_2OH	**89**	100	**95**	86
2	**84**	Valine	$CH(CH_3)_2$	**90**	100	**96**	98
3	**85**	Tryptophan	CH_2-3-Indole	**91**	98	**97**	82
4	**86**	Tyrosine	CH_2-*p*-PhOH	**92**	100	**98**	85
5	**87**	Proline	$CH_2CH_2CH_2$-NCbz	**93**	96	**99**	96
6	**88**	Methionine	$CH_2CH_2SCH_3$	**94**	100	**100**	81

With these in hand, it was the simple case of combining them to generate desired triazole scaffolds **101** to **112** (Table 3.7). For ease of results' analysis and to have a better understanding of each group's contribution to the compound's properties, it was decided to vary either R_1 or R_2, with the other being either a phenyl or a benzyl group. Pleasingly, these all gave moderate to excellent yields.

*Table 3.7: Synthesis of triazoles **101 - 112** with a range of functional groups in the R_1 and R_2 positions: a. i. **52, 95 - 100** (1.0 eq.), **53, 77 - 82** (1.2 eq.), EtOH, 6h, reflux; ii. AcOH, 2h, reflux.*



53, 77 - 82 52, 95 - 100 101 - 112

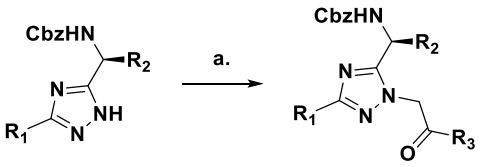
Entry	Starting Materials		R_1	R_2	Yield Triazole (%)	
1	**77**	**52**	$(CH_2)_3CHCH_2$	Bn	**101**	86
2	**78**	**52**	Cyclopropyl	Bn	**102**	81
3	**79**	**52**	*p*-PhCF_3	Bn	**103**	85
4	**80**	**52**	*p*-PhBr	Bn	**104**	91
5	**81**	**52**	*p*-PhOMe	Bn	**105**	87
6	**82**	**52**	CH_2-*p*-PhBr	Bn	**106**	52
7	**53**	**95**	Ph	CH_2OH	**107**	66
8	**53**	**96**	Ph	$CH(CH_3)_2$	**108**	82
9	**53**	**97**	Ph	CH_2-3-Indole	**109**	74
10	**53**	**98**	Ph	CH_2-*p*-PhOH	**110**	83
11	**53**	**99**	Ph	$CH_2CH_2CH_2$-NCbz	**111**	70
12	**53**	**100**	Ph	$CH_2CH_2SCH_3$	**112**	98

Following the previously identified conditions for the alkylation step, potassium carbonate was used as the base, and acetone or DMF as the solvent (Table 3.8). As discussed, for triazoles **101** to **112**, alkylation was carried out with 2-bromoacetophenone, such that R_3 would be a simple phenyl ring. In general, these all proceeded smoothly, with moderate to excellent yields. There were a few exceptions to this for the variations in the R_1 substituent these included **120**, for which R_1 was a cyclopropyl group (Table 3.8, Entry 2), and **124**, for which R_1 was a *p*-bromobenzyl group (Table 3.8, Entry 6). In these cases, the lower yield can be attributed to returning two different alkylated products one of which gave material alkylated at the 2-position of the 1,2,4-triazole, and which therefore would not be able to cyclise. It was hypothesised that this was the case due to the alkyl substituents having smaller steric bulk and therefore substitution in the adjacent positions becoming more favourable. Additionally, the lack of a conjugating group in the R_1-position had the potential to change the electronics of the ring such that alkylation in the adjacent position would be more favourable. For the R_2 substituents, more moderate yields were recorded for **125**, which was descended from serine (Table 3.8, Entry 7), and **128**, which derived from tyrosine (Table 3.8, Entry 11). In both these cases, although alkylation occurred

preferentially on the triazole, some double alkylation also occurred on the free alcohol, however, it was hoped further optimisation of the conditions could limit this undesired reaction if needed on a larger scale.

Beginning from the simple triazole **54** on which the initial optimisation was carried out, it was then necessary to explore the scope of the R_3 position **131** to **136**. The adamantyl was chosen since it represented both alkyl groups and a very bulky substituent, to ensure that sterics would not prohibit cyclisation (Table 3.8, Entry 13). As with the methionine and tryptophan substituents, the inclusion of the thiophene group represented the compatibility of both heterocycles and sulphur heteroatoms (Table 3.8, Entry 14). Moving onto the aryl groups, alongside common biologically relevant functionalities, both an electron withdrawing substituent (*para*-trifluoromethylphenyl) and electron donating substituent (*meta*-methoxyphenyl) were included (Table 3.8, Entries 15 & 16). In the hope of incorporating a functional handle for cross-couplings off the R_3 phenyl ring, *para*-bromophenyl was also included (Table 3.8, Entry 17). Finally, *para*-nitrophenyl was accessed (Table 3.8, Entry 18). The nitro-functionality is often present in a drug discovery context,[204] and would therefore be useful when developing a hit using a SAR approach; in addition, it masked an amine functionality *via* reduction of the nitro.[205] Amino groups are particularly valuable within drug discovery not only as a functional handle, in which they can be used for amide couplings, azide formation and therefore click chemistry and cross-couplings, but also for their hydrogen bond donor properties, which is an important attribute within drug-protein interactions.[69] Therefore, if the conditions cannot be controlled so as to avoid its reduction, it still offers important scope for this work. Pleasingly, all the various alkylations proceeded smoothly with greater than 50% yield.

Table 3.8: Alkylation of the triazole with a range of functional groups in positions R_1, R_2 and R_3: a. ***54, 101-112*** *(1.0 eq.), α-bromoketones* ***55, 113 - 118*** *(1.2 eq.) K_2CO_3 (1.0 eq.), acetone or DMF, 12h, rt.*



54, 101 - 112 **119 - 136**

Entry	Starting Material	R_1	R_2	R_3	Compound	Yield (%)
1	**101**	$(CH_2)_3CHCH_2$	Bn	Ph	**119**	65
2	**102**	Cyclopropyl	Bn	Ph	**120**	53
3	**103**	*p*-PhCF_3	Bn	Ph	**121**	73
4	**104**	*p*-PhBr	Bn	Ph	**122**	83
5	**105**	*p*-PhOMe	Bn	Ph	**123**	77
6	**106**	CH_2-*p*-PhBr	Bn	Ph	**124**	52
7	**107**	Ph	CH_2OH	Ph	**125**	55
8	**108**	Ph	$CH(CH_3)_2$	Ph	**126**	79
9	**109**	Ph	CH_2-3-Indole	Ph	**127**	81
10	**110**	Ph	CH_2-*p*-PhOH	Ph	**128**	33
11	**111**	Ph	$CH_2CH_2CH_2$-NCbz	Ph	**129**	80
12	**112**	Ph	$CH_2CH_2SCH_3$	Ph	**130**	93
13	**54**	Ph	Bn	Adamantyl	**131**	87
14	**54**	Ph	Bn	Thiophene	**132**	61
15	**54**	Ph	Bn	*p*-PhCF_3	**133**	66
16	**54**	Ph	Bn	*m*-PhOMe	**134**	50
17	**54**	Ph	Bn	*p*-PhBr	**135**	82
18	**54**	Ph	Bn	*p*-PhNO_2	**136**	50

With 18 alkylated triazoles in hand, all that remained was to carry out the deprotection and reductive amination (Table 3.9). As expected, the reductive deprotection and amination for those compounds with alkyl substituents in each of the three positions, cyclopropyl, iso-propyl, and adamantyl proceeded smoothly to give the desired bicyclic scaffolds **138**, **144** and **149** in excellent yields (74, 84 and 91% respectively, Table 3.9, Entries 2, 8 & 13). Unsurprisingly, the presence of an alkene functionality within one of these substituents was not tolerated, with the double bond reduced under the reaction

conditions to yield **137** (Table 9, Entry 1); which could be incorporated directly through the use of hexanenitrile for the imidate formation. However, we propose that if required such a functionality could be built in at a later stage through dehydration by early incorporation of an alcohol. This is made possible by the stability of alcohols, both alkyl and aryl, under these conditions as demonstrated by **143** and **146** with yields of 82 and 83% respectively (Table 3.9, Entries 7 and 10).

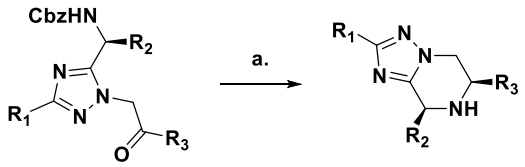
Pleasingly, both electron withdrawing and electron donating groups in both the R_1 and R_3 positions were well tolerated (Table 3.9, Entries 3, 5, 15 & 16). For the *para*-trifluoromethyl phenyl substituents moderate 59% (R_1, **139**) and 71% (R_3, **151**) yields were achieved, for the *para*-methoxyphenyl (R_1, **141**) 77% and for the *meta*-methoxy phenyl (R_3, **152**) 77% were attained, further illustrating the broad scope of this reaction.

The *para*-nitro phenyl group was chosen in the expectation that the nitro would undergo reduction to the aromatic amine concomitantly to the deprotection-cyclisation event (Table 3.9, Entry 18).[206] That allowed us to showcase the potential of this route to generate relevant amine handles from reaction stable, amine-masking functionalities. Pleasingly the reductive deprotection, amination step and nitro reduction proceeded smoothly to yield the amine-bearing scaffold **154** in 71% yield.

Given the presence of the triazole ring within the basic scaffold itself, we did not foresee any problems with the indole group **145** and pyrrolidine-based R_2-group **147**, and indeed these proceeded smoothly with a 93% and 60% yield respectively (Table 3.9, Entries 9 & 11). Although no oxygen-based heterocycles were tested, it was hoped that the tolerance of alcohol groups and methoxy moieties demonstrated their suitability. When reacting sulphur-containing substrates **130** and **132**, the standard conditions were unable to yield the desired cyclised products **148** and **150**; however, as discussed previously, it was hoped that increasing catalyst loading might overcome this (Table 3.9, Entries 12 & 14). Indeed, when increasing palladium-loading to an excess of 2 equivalence we were pleased to register fruitful transformation of **130** into **148**. In the case of thiophene bearing **132**, however, only starting material was recovered even with such an excess of palladium.

Unfortunately, for bromine-bearing substituents, the dehalogenation step was far more rapid than the deprotection, amination sequence, even with lower catalyst loading or lower temperatures. For **122** and **135**, this simply returned the previously synthesised substrate **58**, and therefore no yield was taken (Table 3.9, Entries 4 & 17). For **124**, although dehalogenation was encountered, this returned a novel compound, with an additional methylene unit between the triazole and a phenyl in the R_1 position and this was therefore followed through to yield **142** in a poor 38% yield (Table 3.9, Entry 6).

Table 3.9: Reductive deprotection and amination to give the desired bicyclic scaffold with a range of functional groups in positions R_1, R_2 and R_3: a. ***119 - 136*** *(1.0 eq.), $NH_4{\cdot}CO_2H$ (30 eq.), $Pd(OH_2)/C$ (20 mol %), $CH_3OH{:}H_2O$ (3:1 v/v), 12h, rt.*



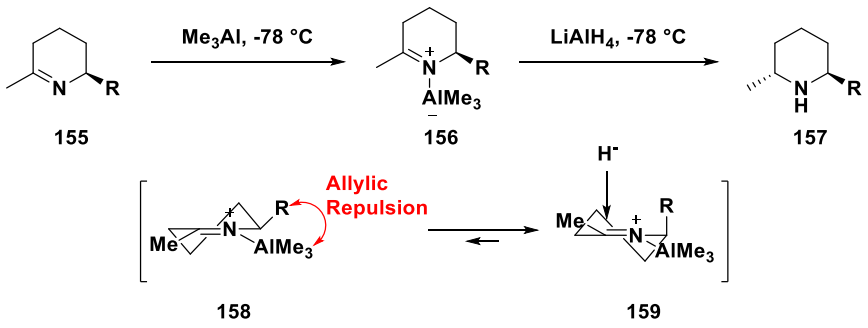
119 - 136 137 - 154

Entry	Starting Material	R_1	R_2	R_3	Compound	Yield (%)	d.r.
1	**119**	$(CH_2)_4CH_3$	Bn	Ph	**137**	60[a]	>20:1
2	**120**	Cyclopropyl	Bn	Ph	**138**	74	>20:1
3	**121**	*p*-PhCF_3	Bn	Ph	**139**	59	>20:1
4	**122**	*p*-PhBr	Bn	Ph	**140**	n/a[b]	>20:1
5	**123**	*p*-PhOMe	Bn	Ph	**141**	77	>20:1
6	**124**	Bn	Bn	Ph	**142**	38[c]	>20:1
7	**125**	Ph	CH_2OH	Ph	**143**	82	>20:1
8	**126**	Ph	$CH(CH_3)_2$	Ph	**144**	84	>20:1
9	**127**	Ph	CH_2-3-Indole	Ph	**145**	93	>20:1
10	**128**	Ph	CH_2-*p*-PhOH	Ph	**146**	83	>20:1
11	**129**	Ph	$(CH_2)_3$-NH	Ph	**147**	60	>20:1
12	**130**	Ph	$(CH_2)_3SCH_3$	Ph	**148**	51[d]	>20:1
13	**131**	Ph	Bn	Adamantyl	**149**	91	>20:1
14	**132**	Ph	Bn	Thiophene	**150**	0[d,e]	n/a
15	**133**	Ph	Bn	*p*-PhCF_3	**151**	71	>20:1
16	**134**	Ph	Bn	*m*-PhOMe	**152**	77	>20:1
17	**135**	Ph	Bn	*p*-PhBr	**153**	n/a[b]	>20:1
18	**136**	Ph	Bn	*p*-PhNH_2	**154**	71[f]	>20:1

a. Reduction of the double bond was observed in the product, yield refers to cyclised product bearing a n-pentyl chain as R_1; b. Dehalogenation was observed, product not isolated; c. Dehalogenation was observed, yield refers to cyclised product bearing a benzyl group as R_1; d. 2 eq. of $Pd(OH)_2$; e. Material remained as starting material; f. Reduction of the nitro was observed in the product, yield refers to cyclised product bearing a p-aminophenyl as R_3.

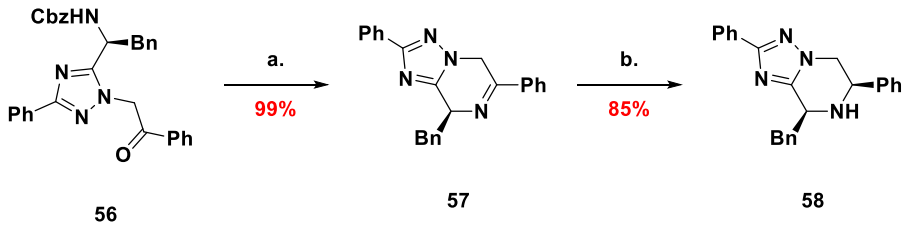
3.1.3. Studies Towards the Trans-diastereomer

In order to take advantage of the modular nature of the route designed, it was hoped that the *trans*-diastereomer could be achieved from common intermediate **69** (Scheme 3.8). It was assumed that the *cis*-diastereomer was always formed preferentially as a result of the axial hydride attack into the most stable half-chair of the imine intermediate. Therefore, it was hoped that by performing the reduction in the presence of a bulky Lewis acid, the natural stereoselective preference could be overcome. In this case, coordination of the nitrogen to a Lewis acid, such as trimethylaluminium, would shift the equilibrium towards the less favoured half-chair conformation, in which the R group lies axial, as this would minimise the allylic repulsion between the R group and the Lewis acid. As a result, axial hydride attack would lead to the trans-product (Scheme 3.9). A search of the literature highlighted a number of examples in which 2,6-*trans*-disubstituted piperidines **157** were generated in this way.[139–141,207–212] No examples were found for piperazine rings, however it was hoped that they might behave in a similar way.



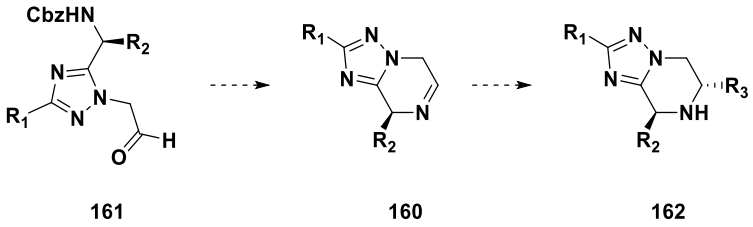
Scheme 3.9: Scheme to demonstrate the possible use of Lewis acids to access the trans-diastereomer. Figure adapted from reference.[210]

In order to generate the imine, substrate **56** was stirred in hydrogen bromide, and to avoid aromatisation was quenched with diethyl ether as soon as the starting material had been consumed; as a result, imine **57** was isolated in a 99% yield. The imine was reacted on crude, at -78 °C, by the addition of trimethylaluminium, followed by lithium aluminium hydride. The product was isolated in a good yield after stirring overnight; however, NMR analysis revealed that the *cis*-diastereomer **58** had been formed (Scheme 3.10). We hypothesised that, compared to the literature examples, in which the two substituents are either alkyl chains or simple methyl groups, the preference for the bulkier benzyl group to lie equatorial overcomes the allylic repulsion.



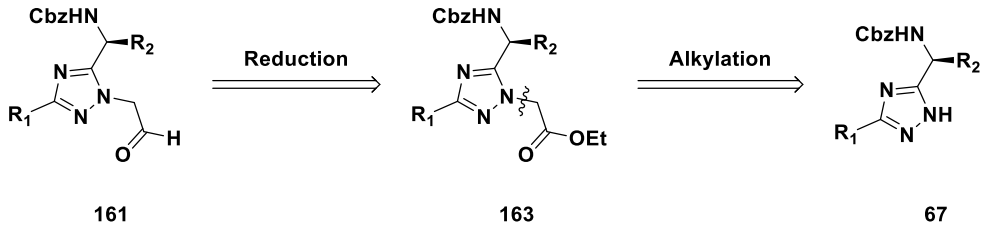
Scheme 3.10: Attempted synthesis of the trans-diastereomer using a Lewis acid to change the natural selectivity: a. ***56*** *(1.0 eq.), HBr (33 wt% in AcOH, excess), 30 mins, rt, 99%* ***57****; b.* ***57*** *(1.0 eq.), $AlMe_3$ (2.0 eq.), $LiAlH_4$ (1.0 eq.), THF, 12h, -78 °C to -20 °C, 85%* ***58****.*

By this reasoning, replacing the benzyl group with a sterically less demanding group would provide access to the *trans*-diastereomer, however this would result in restricting the scope of this methodology. As a result, it was proposed that a route was needed which would harness the natural bias of the substrate. One such possibility would be to generate imine **160** from the corresponding aldehyde **161**: as a result, axial attack of a nucleophile, such as a Grignard reagent, would give the desired *trans*-diastereomer **162** (Scheme 3.11).



Scheme 3.11: Proposed route to take advantage of the natural stereoselective bias of the substrate.

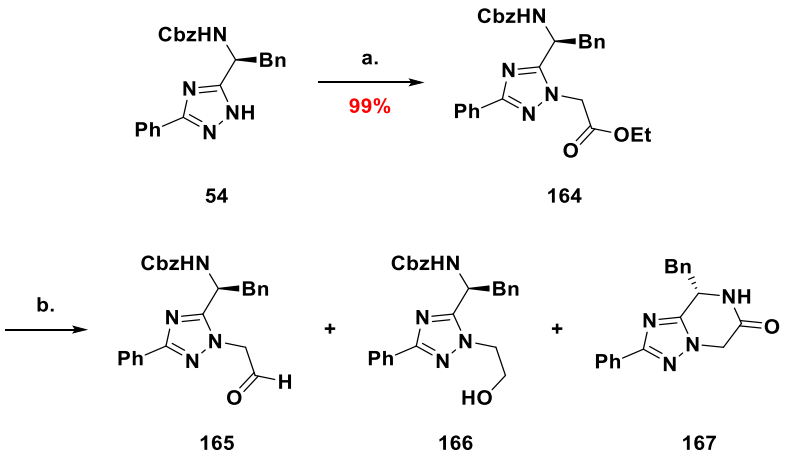
To this end, it was anticipated that the desired aldehyde **161** could be generated by reduction of ester **163**, which in turn could be synthesised from the same triazole scaffold **67** used in the synthetic route towards the *cis*-diastereomer. (Scheme 3.12).



Scheme 3.12: Proposed retrosynthetic route from the desired aldehyde to the triazole used in the cis-diastereomer synthesis

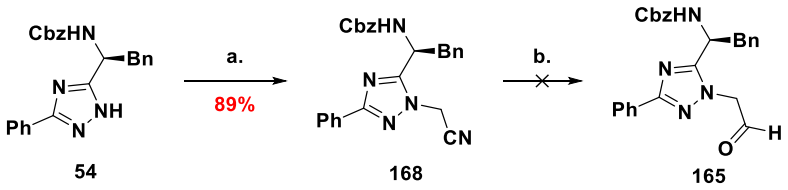
Therefore, using the simplest substituents, in which R_1 is a phenyl ring and R_2 is a benzyl group, triazole **54** was alkylated with ethyl 2-bromoacetate. This proceeded smoothly in excellent yield following the conditions used for the equivalent ketones in the synthesis of the *cis*-diastereomer. It was hoped that diisobutylaluminium hydride (DIBAL) could be used to selectively reduce the ester to the aldehyde,

without over reduction to the alcohol, however, this generated a mixture of the ester **164**, the aldehyde **165**, the alcohol **166** and the amide **167** formed as a result of the deprotection of the nitrogen (Scheme 3.13).



*Scheme 3.13: Attempted synthesis of aldehyde **165** via the ester **164:** a. **54** (1.0 eq.), ethyl-2-bromoacetate (1.2 eq.), K_2CO_3 (1.0 eq.), acetone, 12h, rt, 99% **164**; b. **164** (1.0 eq.), DIBAL (1.1 eq.), toluene, 3h, -78 °C.*

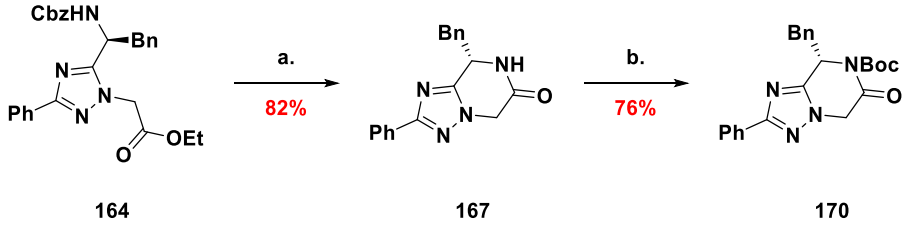
In an attempt to avoid the over-reduction of the ester, it was proposed to instead attempt to generate the aldehyde from the corresponding nitrile **168**. First, alkylation of triazole **54** would need to be carried out, this time with bromoacetonitrile, which pleasingly proved to have broad applicability and provided scaffold **168** in 89% yield. Once again, the reduction was attempted using DIBAL, a methodology with excellent precedence.[213] Unfortunately, for this scaffold it gave a complex mixture of products (Scheme 3.14).



*Scheme 3.14: Attempted synthesis of aldehyde **165** via the nitrile **168:** a. **54** (1.0 eq.), bromoacetonitrile (1.2 eq.), K_2CO_3 (1.0 eq.), acetone, 12h, rt, 89% **168**; b. **168** (1.0 eq.), DIBAL (1.2 eq.), Et_2O, 1h, 0 °C.*

Given that the aldehyde appeared to be inaccessible *via* reduction, alternative routes were considered. A literature search demonstrated that it was possible to form an imine by the controlled reduction of an amide, particularly for cyclic systems.[214–217] To this end, the lactam could be generated spontaneously from the previously synthesised ester **164** by deprotection of the primary amine. The deprotection was carried out using hydrogen and palladium on carbon, to yield lactam **167** in excellent yield. When considering the possible conditions for reduction of the resultant amide **167** to the corresponding imine **169**, the majority of methods required the amide to be *tert*-butyloxycarbonyl (Boc) protected,[215–217] although there was some suggestion this might not be necessary.[214] To this end, some of lactam **167**

was carried forward in a Boc protection, to form **170** in good yield, whilst the rest was retained as the unprotected lactam **167** (Scheme 3.15).



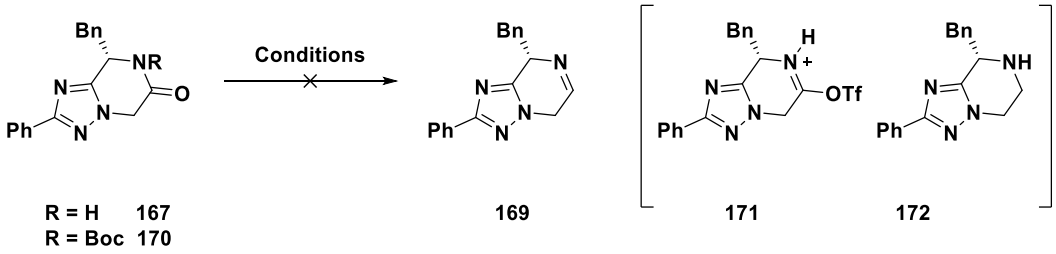
164 167 170

*Scheme 3.15: Synthesis of the Lactam **167** and Boc-protected Lactam **170** from the ester **164:** a. **164** (1.0 eq.), H_2, Pd/C (10 mol %), CH_3OH, 3h, rt, 82% **167**; b. **167** (1.0 eq.), Boc_2O (1.5 eq.), DMAP (0.5 eq.), AcCN, 12h, rt, 76% **170**.*

With the amide **167** and Boc-protected amide **170** in hand, the partial reduction of the lactam to the imine was attempted (Table 3.10). There was considerable precedent for this step using lithium triethylborohydride or "superhydride" as it is often referred to (Table 3.10, Entries 1 and 2). For the protected lactam **169**, LCMS data suggested that whilst the imine had formed, it had reacted with itself. Meanwhile for the unprotected lactam **167**, no reaction occurred, with the starting material recovered. Following on from this lack of success, a paper from Pelletier *et al.* was identified, in which they explored the controlled and chemoselective reduction of secondary amides.[218] They proposed that the use of a less nucleophilic hydride source would prevent reduction all the way to the amine, enabling isolation of the reactive imine. The conditions they developed, also supported by other groups' reports,[219] used a one-pot secondary amide activation using triflic anhydride and 2-fluoropyridine and selective reduction with triethylsilane (Table 3.10, Entry 3 and 4). Unfortunately, for this system, whilst the triflation proceeded smoothly, the material was not reduced, leaving **171**. In an attempt to drive the reduction, the procedure was repeated using the superhydride reductant; but this gave over-reduction to the undesired amine **172** (Table 3.10, Entry 4).

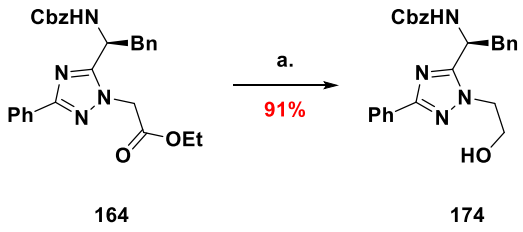
Having exhausted the metal-free routes to accessing the imine **169**, the use of metal reductants was explored. The use of catalytic iridium and diethylsilane for the reduction of secondary amides to imines had been reported by Cheng *et al.*,[220] however a mixture of products was generated including, amine **172** and the same dimer **173** seen for the Boc-protected reduction, along with a substantial amount of starting material, as identified by LCMS data (Table 3.10, Entry 5). Finally, a common literature procedure for this step involving the use of Schwarz reagent[221,222] was tested, however, this failed to generate the imine, with the starting material returned (Table 3.10, Entry 6).

Table 3.10: Testing of conditions for the reduction of the lactam to a cyclic imine.



Entry	Starting Material	Conditions	Yield (%)	Result
1	**170**	$LiEt_3BH$, THF, 12h, -25 °C to rt	0	**173**
2	**167**	$LiEt_3BH$, THF, 12h, -25 °C to rt	0	**167**
3	**167**	2-fluoropyridine, Tf_2O, Et_3SiH, THF, 12h, -78 °C to rt	0	**171**
4	**167**	2-fluoropyridine, Tf_2O, $LiEt_3BH$, THF, 12h, -78 °C to rt	-	**171 & 172**
5	**167**	$[Ir(COE)_2Cl]_2$, Et_2SiH_2, CH_2Cl_2, 12h, rt	-	**167, 169, 172, 173**
6	**167**	$Cp_2Zr(H)Cl$, THF, 12h, -25 °C to rt	0	**167**

With the over-reduction of the lactam to the amine proving to be a considerable problem, we returned to the synthesis of the aldehyde. Given that aldehyde **165** proved inaccessible under reductive conditions, it was proposed that it might instead be formed by oxidation from the corresponding primary alcohol. This in turn could be formed by reduction from ester **164**, which was carried out successfully in an excellent 91% yield using lithium borohydride (Scheme 3.16).

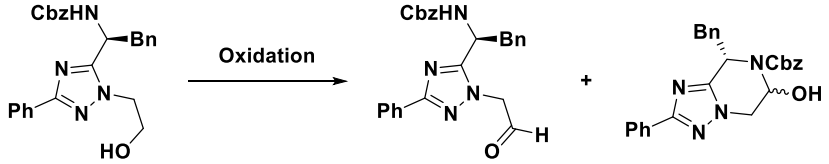


*Scheme 3.16: Reduction of the ester **164** to the corresponding alcohol **174**: a. **164** (1.0 eq.), $LiBH_4$ (1.2 eq.), Et_2O, 3h, 0 °C to rt, 91% **174**.*

With the alcohol **174** in hand, oxidative conditions for the formation of the aldehyde **165** were explored (Table 3.11). The first conditions tested were the Swern conditions,[223,224] since these offered no risk of over oxidation and were sufficiently mild as to be highly compatible with other functionalities, but this gave an inseparable mixture of products (Table 3.11, Entry 1). Following on from this, Dess-Martin

periodinane[225,226] conditions similarly gave an inseparable mixture of products (Table 3.11, Entry 2). Graves *et al.* proposed using Oppenauer chemistry for the aluminium catalysed selective oxidation of alcohols, however this simply returned starting material (Table 3.11, Entry 3). Given the mildness of the conditions, we returned at this point to hypervalent iodide, in the hope that changing the reagent or solvents might enable isolation of the desired aldehyde. 2-Iodoxybenzoic acid (IBX) is a mild oxidising agent for alcohols, and following the procedure from Frigerio *et al.* this was trialled in DMSO,[227] yielding a complex mixture of products once again (Table 3.11, Entry 4). Finally, Bartlett and Beaudry used IBX in ethyl acetate to form *β*-diketones from *β*-hydroxyketones, and given the *β*-relationship between the hydroxyl and the triazole ring,[228] we hoped these conditions might prove successful for our structure. This proved to be the case, although the aldehyde was not isolated, instead it was found that upon aldehyde formation, the Cbz-protected amine reacted with this highly reactive functional group, thus generating the hemi-aminal **175**. It was hoped that this could be used in the same way as the aldehyde to generate the imine (Table 3.11, Entry 5).

*Table 3.11: Testing of conditions for the oxidation of the primary alcohol **174** to the corresponding aldehyde **165**.*

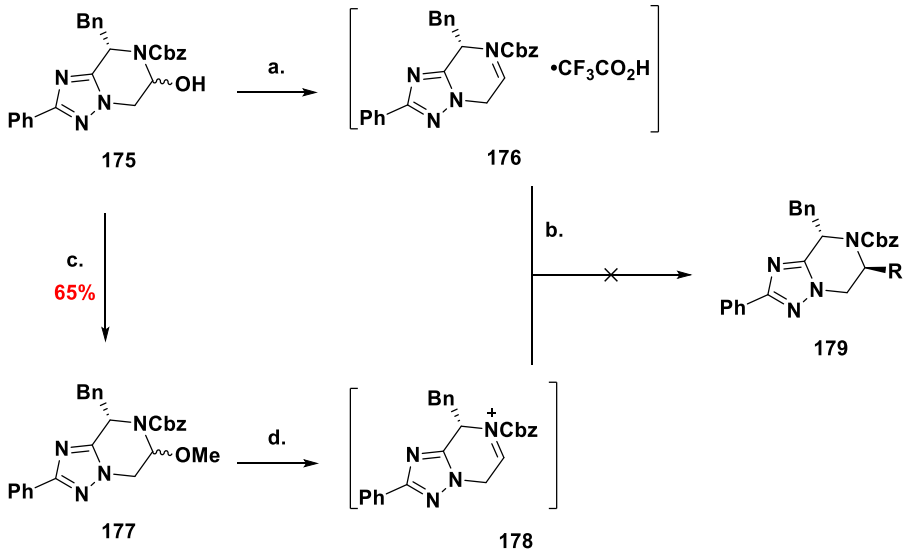


174 **165** **175**

Entry	Conditions	Yield X (%)	Result
1	$COCl_2$, DMSO, DIPEA, 3h, -78 °C - rt	0	Complex Mixture
2	DMP, CH_2Cl_2, 12h, rt	7	Complex Mixture
3	$AlMe_3$, 3-nitrotoluene, 12h, rt	0	**174**
4	IBX, DMSO, 3h, rt	0	Complex Mixture
5	IBX, EtOAc, 12h, reflux	99	**175**

A literature search suggested the iminium salt could be formed, with the Cbz group still present, and it was hoped that this would be more stable than the free imine, removing the possibility of dimerization (Scheme 3.17). The addition of trifluoroacetic acid could be used to trigger the generation of the iminium triflate salt **176**, which was generated *in situ*.[229] Addition of allyl magnesium chloride,[230] unfortunately removed the Cbz-protecting group and therefore enabled dimerization of the highly reactive imines. In an attempt to avoid this, it was proposed to use a softer nucleophile that would not be sufficiently reactive as to remove the Cbz-protecting group. To this end, first the aminal **177** was generated from hemiaminal **175** using *p*-toluene sulfonic monohydrate in moderate yield.[231,232] From this, it was proposed that the imine could be generated in the presence of a cuprate, such that the unstable

iminium ion would immediately be quenched with the soft nucleophile.[233,234] Unfortunately, this returned only starting material.



Scheme 3.17: Attempts at generating the trans-diastereomer ***178****: a.* ***175*** *(1.0 eq.), TFA (excess), CH_2Cl_2, 12h, rt; b. allyl magnesium chloride (4.0 eq.), CH_2Cl_2, 12h, -78 °C to rt; c.* ***175*** *(1.0 eq.), p-toluene sulfonic acid monohydrate (0.1 eq.), CH_3OH, 12h, rt, 65%* ***177****; d. i. CuBr·Me_2S (3.0 eq.), PhMgBr (3.0 eq.), Et_2O, 1h, -40 °C, ii. BF_3·OEt_2 (3.0 eq.)* ***177*** *(1.0 eq.) 12h, -78 °C to 0 °C.*

These rounds of optimisation showed that a delicate balance of reactivities would be needed to generate the *trans*-diastereomer from the iminium ion (*e.g.* a nucleophile finely tuned so as not to be too reactive and cleave the Cbz-group, but reactive enough so as to attack the iminium ion). We identified this as a major drawback in our quest for a general approach to synthesising a library of these molecules, therefore we sought an alternative route that could provide better scope, tolerance and selectivity.

To this end, we considered whether the *trans*-diastereomer could be accessed from the *cis*-diastereomer in a controlled manner. It was proposed that if the nitrogen from the *cis*-diastereomer were to be protected with a bulky group, upon regeneration of the imine the bulky protecting group would lie on the opposite face to the pre-existing chiral centre (Figure 3.4). It was therefore hoped that reduction of this iminium ion would occur from the opposite face compared to the *cis*-formation as a result of the steric bulk of the protecting group, thus overcoming the natural bias of the substrate and generating the desired *trans*-diastereomer.

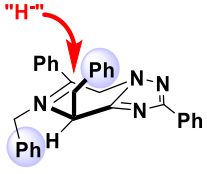
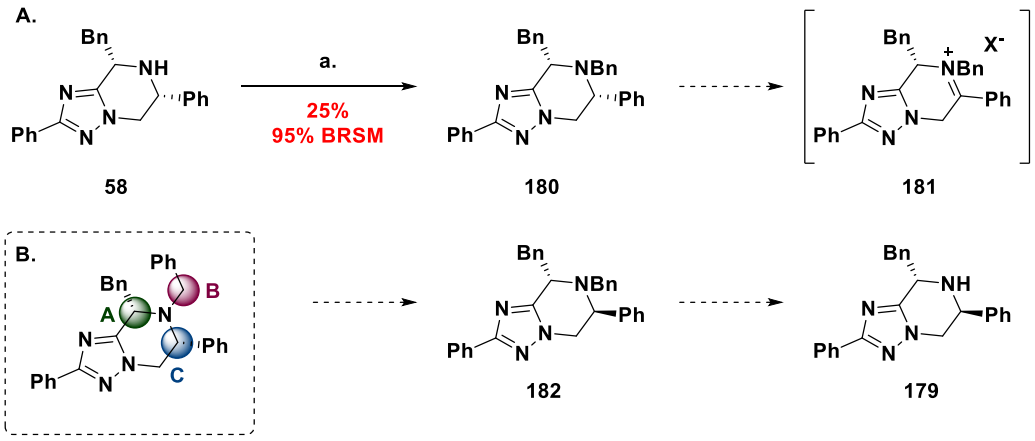


Figure 3.4: Diagram illustrating the proposed mechanism behind the controlled inversion of a single stereocentre.

Significant work has been carried out on the selective oxidation of tertiary amines to the corresponding iminium ions. This includes the use of ruthenium catalysts for the visible light photocatalytic oxidation of tertiary amines,[235–239] oxidation to the *N*-oxide using *meta*-chloroperoxybenzoic acid (mCPBA) followed by treatment with trifilic anhydride,[240,241] or oxidation with *N*-bromosuccinimide (NBS),[242–244] cerium ammonium nitrate (CAN)[245] or tropylium bromide.[246]

We proposed to utilise this work to generate the iminium ion, such that it could be reduced to give the desired *trans*-diastereomer. To this end, the secondary amine from *cis*-diastereomer **58** was protected with a benzyl group to generate the required tertiary centre (Scheme 3.18: a). As a result of the steric crowding around this position, this was low yielding, however this was not deemed to be a problem since the starting material was recovered. Work on the final three steps is ongoing.

There are multiple positions in this molecule at which the proton could be lost/abstracted (Scheme 3.18: b), provided it occurs at either A or C, a desired *trans*-diastereomer would be generated. In order to definitively determine the stereochemistry x-ray crystallography and NOE studies will be required on the final scaffold.

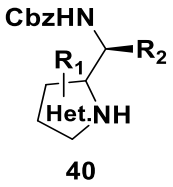


Scheme 3.18: A. Synthesis of the trans-diastereomer via stereocentre inversion: a. ***58*** *(1.0 eq.), BnBr (3.0 eq.), K_2CO_3 (3.0 eq.), DMF, 12h, rt, 25%, 95% BRSM* ***180****; B. Possible positions for proton loss for the generation of the iminium ion.*

3.1.4. Studies towards Other Heterocycles.

Having established the accessibility of the *cis*-diastereomer for the triazole-based scaffold, it was hoped that the modular synthetic route could be applied more generally to a range of different heterocycles. Variations in the position of nitrogens and the nature of heterocycles is often a key step in hit to lead optimisation, and as such, ease of access is particularly important in demonstrating the utility of this route for drug discovery.

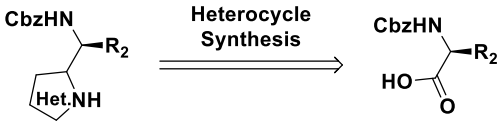
The first step for all potential heterocycle-based scaffolds was the synthetic tractability of the heterocycle with the pendant carboxybenzyl-protected nitrogen **40**, preferentially with a pre-formed chiral centre (Figure 3.5). Whilst ideally this pre-formed chiral centre would be incorporated from the chiral pool, a racemate of the cis-diastereomer would be obtained if that were not possible. This event would still lead to a relevant series of compounds for testing, which could be synthesised in their enantiomerically pure form at a later stage, if a hit were to be identified from screening.



40

Figure 3.5: Proposed heterocyclic scaffolds required for the application of our newly designed modular route.

Given the nature of the described pendant functional group, and the common approaches to heterocycle synthesis involving esters, ketones and amides, it was hoped that the synthesis of all heterocycles could revolve around amino acids (Scheme 3.19). The advantage of this would be two-fold: it would give access to a huge pool of potential functionalities in the R_2 position, both natural and unnatural; and it would provide cheap and readily available enantiopure starting materials.

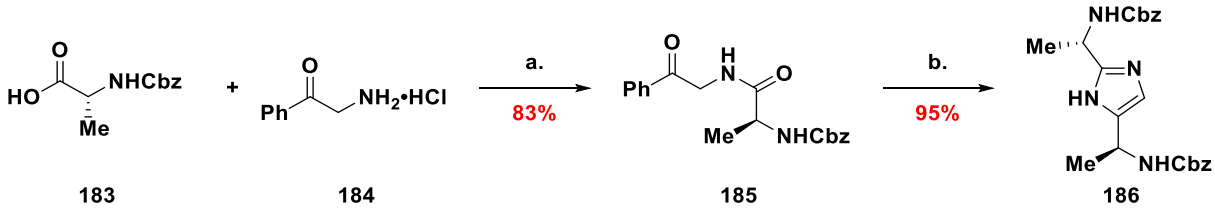


40 **62**

Scheme 3.19: Retrosynthetic analysis of the desired heterocyclic scaffold to be synthesised from carboxybenzyl-protected amino acids.

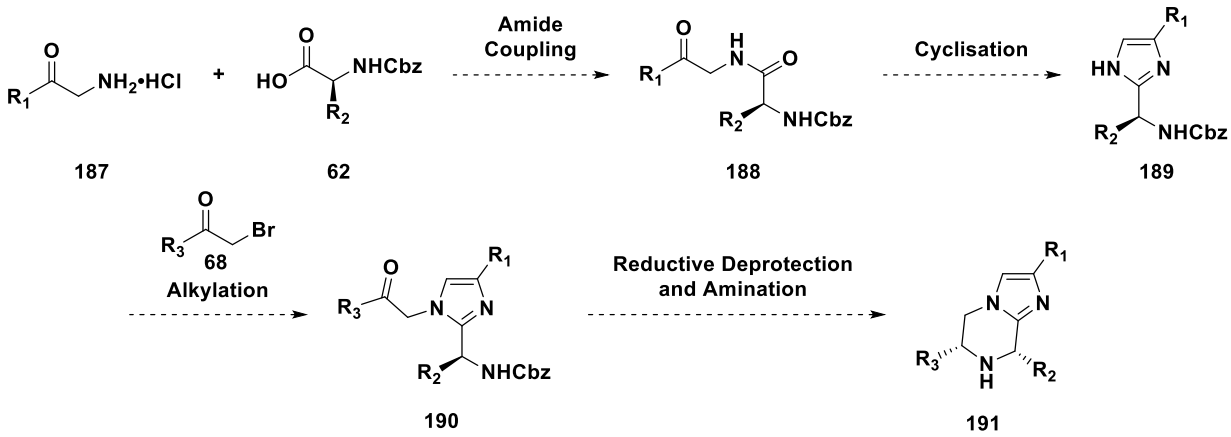
3.1.4.1. Imidazole

The first heterocycle that was tackled was the imidazole-based scaffold. The first step was to identify the manner in which the initial heterocyclic-scaffold based on **40** could be accessed. After identifying suitable literature examples to generate similar scaffolds,[247–251] we decided to concentrate on the most step efficient example, described by Breslin *et al.*[248,249] in which an amide coupling between Cbz-*L*-Alanine **183** and 2-aminoacetophenone hydrochloride **184**, followed by heating in ammonium acetate of the amide coupled product **185**, yielded the desired imidazole **186** in 79% over two steps (Scheme 3.20).



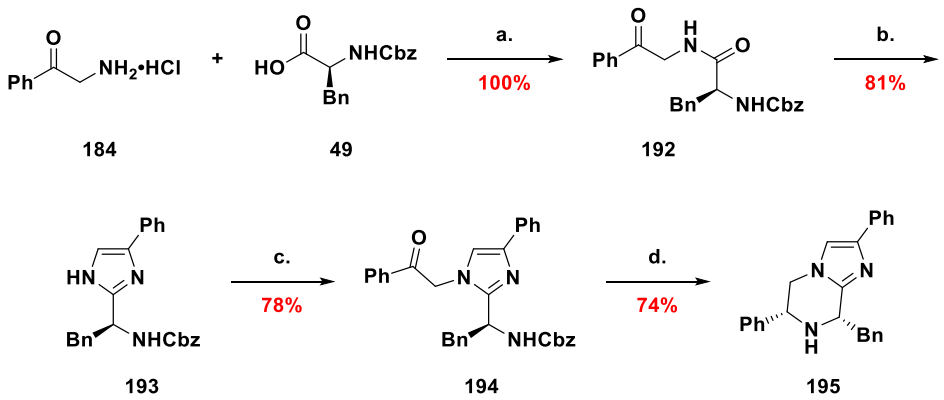
Scheme 3.20: Synthetic route carried out by Breslin et al. in the construction of imidazole scaffolds: *a. Cbz-L-Alanine* ***183****, 2-aminoacetophenone hydrochloride* ***184****, EDC, HOBt, NMM, CH_2Cl_2, 83%* ***185****; b.* ***185****, NH_4OAc, AcOH, reflux, 95%* ***186****.*[248]

This synthetic route was then applied to the synthesis of imidazole-based partially saturated 5,6 bicyclic scaffolds (Scheme 3.21). This was proposed to proceed first with an amide coupling between an *α*-aminoketone hydrochloride salt **187** and a carboxybenzyl-protected amino acid **62**. A cyclisation of the amide coupled product **188** would generate the required imidazole **189**, from which an alkylation would introduce the third R group in preparation for the reductive deprotection and reductive amination of **190** to form the imidazole-based bicyclic scaffold **191**.



Scheme 3.21: Proposed route for the synthesis of an imidazole based scaffold.

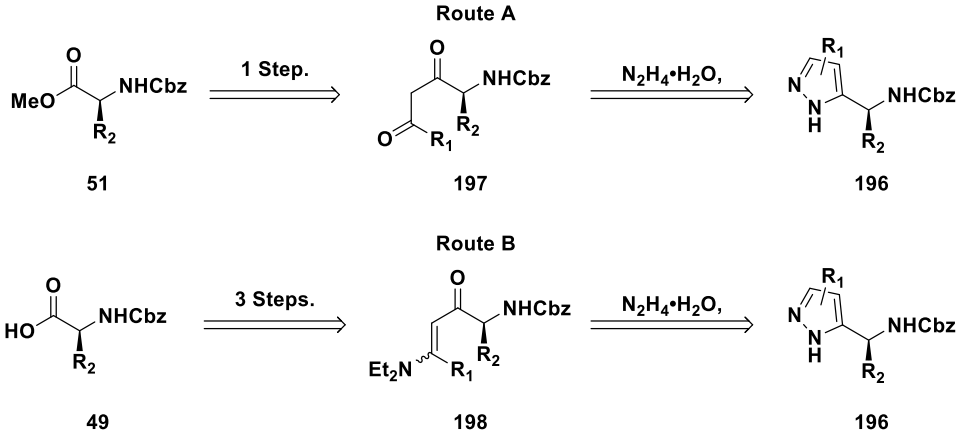
To demonstrate the feasibility of this route to deliver the desired scaffold, the synthesis was applied to a simple scaffold in which R_1 and R_3 were unsubstituted phenyl rings and R_2 a benzyl group (Scheme 3.22). The amide coupling proceeded smoothly, using EDC, HOBt and NMM, to yield **192** in quantitative yield on a multi-gram scale. The cyclisation of amide **192** to the imidazole proved a little more challenging, the conditions used to generate imidazole **186** (Scheme 1.20) only provided a low 36% yield of desired product **193**. Further examination of the literature suggested that use of acetic acid as the solvent would be unnecessary, and the less reactive xylenes would be sufficient.[250,251] Gratifyingly, this proved to be the case, and the imidazole **193** was generated in an excellent 81% yield on gram scale by refluxing with ammonium acetate in xylenes. From **193**, alkylation of the nitrogen using potassium carbonate in acetone, gave an excellent yield of **194**, in preparation for the final diastereoselective step. Palladium dihydroxide and ammonium formate yielded the desired 5,6-bicyclic scaffold in an excellent 74% yield and >20:1 diastereoselective ratio.



Scheme 3.22: Synthesis of an example of an imidazole-based scaffold, with R_1 = Ph, R_2 = Bn, R_3 = Ph, ***195****: a.* ***49*** *(1.0 eq.),* ***184*** *(1.0 eq.), EDC (1.05 eq.), HOBt (1.05 eq.), NMM (1.05 eq.), CH_2Cl_2, 3h, 0 °C to rt, 100%* ***192****; b.* ***192*** *(1.0 eq.) NH_4OAc (10.0 eq.), xylene, 8h, reflux, 81%* ***193****; c.* ***193*** *(1.0 eq.), 2-bromoacetophenone* ***55*** *(1.2 eq.), K_2CO_3 (1.0 eq.), 12h, rt, 78%* ***194****; d.* ***194*** *(1.0 eq.), $NH_4{\cdot}CO_2H$ (30 eq.), $Pd(OH_2)$/C (20 mol%), CH_3OH:H_2O (3:1 v/v), 12h, rt, 74%, >20:1 d.r.* ***195****.*

3.1.4.2. Pyrazole

Following the illustration of the applicability of the designed route to the imidazole-based scaffold, it was hoped that similar success could be found for the pyrazole-based scaffold. There are a number of approaches to the construction of pyrazole-based scaffolds **196** (Scheme 3.23), of which the two most common generate the pyrazole through addition of hydrazine into (i) a 1,3-dicarbonyl **197** (Scheme 3.23, Route A)[146,154,252] and (ii) an *α,β*-unsaturated ketone **198** (Scheme 3.23, Route B).[253,254] The 1,3-dicarbonyl **197** could be synthesised from the amino ester **51** in a single step, the *α,β*-unsaturated ketone **198** in three steps from the amino acid **49**.

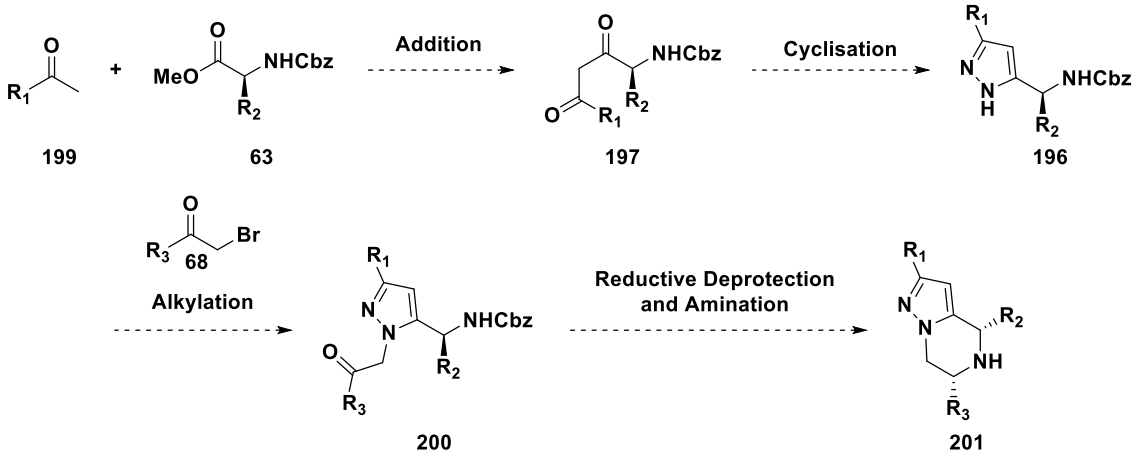


51 197 196

49 198 196

Scheme 3.23: Retrosynthetic analysis of the required pyrazole scaffold for the pyrazole-based 5,6-bicyclic scaffold.

Given that route A would be more step efficient, this was first explored (Scheme 3.24). Overall, the proposed route began with the addition of the enol of a ketone **199** into the relevant Cbz-*L*-amino ester **63**, to form the 1,3-dicarbonyl **197** necessary for pyrazole synthesis. Addition of hydrazine across the 1,3-dicarbonyl **197** would thus generate **196**, for which alkylation followed by reductive deprotection and amination would give the desired scaffold.



199 63 197 196

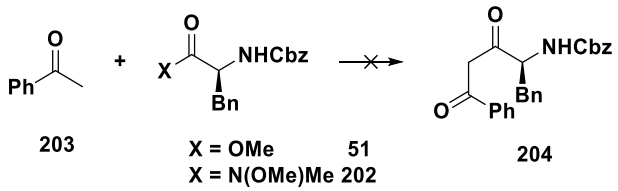
68

200 201

Scheme 3.24: Proposed route to access the pyrazole-based 5,6 partially saturated scaffold.

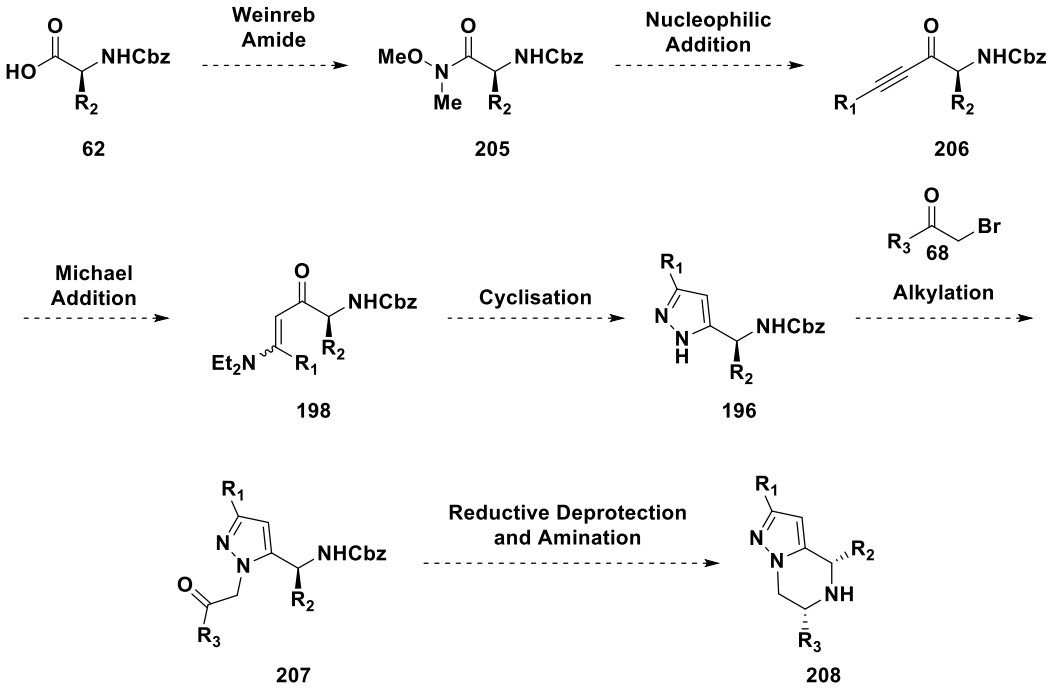
To illustrate the tractability of this proposed route, the synthesis was applied to a simple scaffold in which R_1 and R_3 were unsubstituted phenyl rings and R_2 a benzyl group. Initially it was necessary to identify conditions for the single addition of the enolate of acetophenone into the amino ester of Cbz-*L*-phenylalanine **51**, synthesised previously for the construction of the triazole-based scaffolds (Table 3.12). Potassium bis(trimethylsilyl)amide[255] (Table 3.12, Entry 1) and the much more basic lithium diisopropylamide[256] (Table 3.12, Entry 2) were tested with **51**, however only starting material was recovered. More commonly for these additions, Weinreb amides are used to remove the risk of double addition,[257,258] so the Weinreb amide **202** was also tested, with the much milder potassium *tert*-butoxide[259] (Table 3.12, Entry 3) and the strongly basic butyl lithium[260] (Table 3.12, Entry 4). Disappointingly, only unreacted starting material was detected after 24 hours, and therefore the stepwise approach was attempted instead (scheme 1.23, Route B).

Table 3.12: Exploration of conditions for the single addition of the enolate of acetophenone into the amino ester of Cbz-L-phenylalanine: ***51*** *or* ***202*** *(1.0 eq.), Acetophenone* ***203*** *(1.5 eq.), see table for conditions.*



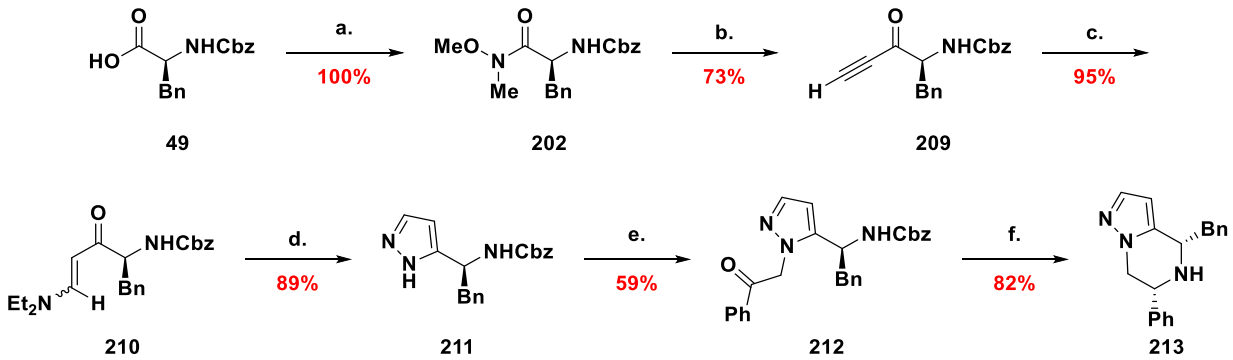
Entry	X	Conditions	Yield	Outcome
1	OMe	KHMDS (1.6 eq.), THF, 0 °C to rt	0	Starting Material
2	OMe	LDA (1.6 eq.), THF, -20 °C to rt	0	Starting Material
3	N(OMe)Me	KO^{t}Bu (1.6 eq.), THF, 0 °C to rt	0	Starting Material
4	N(OMe)Me	^{n}BuLi (3.5 eq.), THF, 0 °C to rt	0	Starting Material

When considering the synthesis of pyrazole **196** through addition of hydrazide into an *α,β*-unsaturated ketone **198**, first synthesis of **198** needed to be explored. From the literature, came the proposed route from the amino acid starting material **62** (Scheme 3.25).[253,254] Conversion to the Weinreb amide **205** would enable a single nucleophilic addition to generate the *α,β*-unsaturated ketone **206**; a Michael addition into the alkyne with diethylamine would give **198**, such that pyrazole **196** could be formed by addition of hydrazine. The final two steps would follow the previously described alkylation, reductive deprotection and amination sequence (Scheme 3.8) to give the partially saturated 5,6-bicycle **208**.



Scheme 3.25: Proposed synthetic route to pyrazole-based Scaffolds.

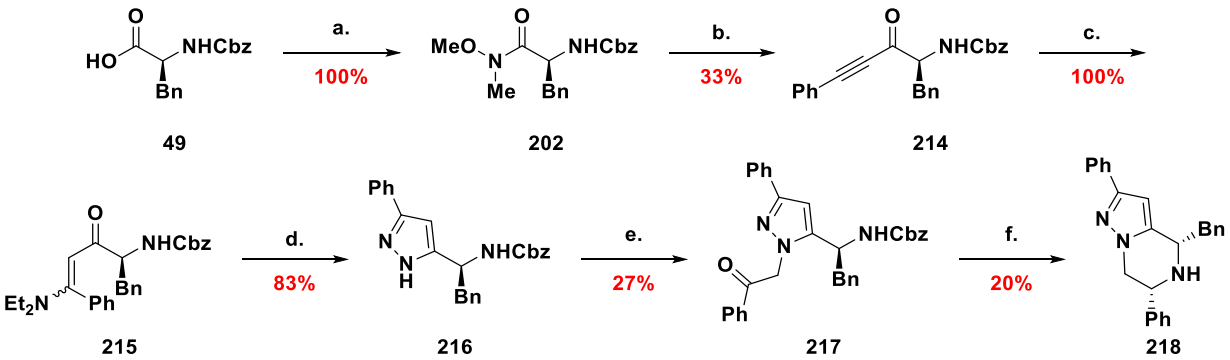
Following the literature precedent, an example was synthesised in which the pyrazole ring was unsubstituted, whilst R_2 and R_3 remained the simple benzyl and phenyl groups respectively, with the assumption that they could be substituted for other groups, as illustrated for the triazole scaffold. Formation of the Weinreb amide **202** from *Cbz-L*-phenylalanine **49** proceeded quantitatively on multi-gram scale. Addition into amide **202** with ethynyl magnesium bromide gave a good yield at 73%, and this was followed by the high yielding Michael addition with diethylamine. Pyrazole formation by refluxing the *α,β*-unsaturated ketone **210** with hydrazine and acid gave an excellent 89% yield. The alkylation proved more problematic, with the material remaining as starting material, however, it was found that changing the base from potassium carbonate to *N,N*-diisopropylethylamine and the solvent to tetrahydrofuran from acetone enabled a 59% yield to be achieved.[261] The final step proceeded smoothly with an excellent 82% yield and >20:1 diastereoselectivity.



Scheme 3.26: Synthesis of an example of a pyrazole-based scaffold with R_1 = H, R_2 = Bn, R_3 = Ph, ***213****: a.* ***49*** *(1.0 eq.), HNMeOMe.HCl (1.5 eq.), HOBt (1.1 eq.), HBTU (1.1 eq.) DIPEA (2.6 eq.), CH_2Cl_2, 12h, rt, 100%* ***202****; b.* ***202*** *(1.0 eq.), ethynyl magnesium bromide (4.5 eq.), THF, 12h, -78 °C to rt, 73%* ***209****; c.* ***209*** *(1.0 eq.), $HNEt_2$ (1.1 eq.), CH_2Cl_2, 12h, rt, 95%* ***210****; d.* ***210*** *(1.0 eq.), $N_2HN_2H{\cdot}H_2O$ (1.1 eq.), HCl (aq) (1.1 eq.), 3h, reflux, 89%* ***211****; e.****211*** *(1.0 eq.), 2-bromoacetophenone* ***55*** *(1.2 eq.), DIPEA (1.0 eq.), THF, 12h, rt, 59%* ***212****; f.* ***212*** *(1.0 eq.), $NH_4{\cdot}CO_2H$ (30 eq.), $Pd(OH_2)/C$ (20 mol%), $CH_3OH{:}H_2O$ (3:1 v/v), 12h, rt, 82%, >20:1 d.r.* ***213****.*

The successful synthesis for the unsubstituted pyrazole scaffold was encouraging; however, in order to maximise the potential vectors incorporated into the scaffold, it was important to ensure that pyrazole substitution wouldn't affect the designed route. This was particularly important for the pyrazole, since alkylation could take place on either of the two nitrogen atoms, but only alkylation on one would enable formation of the final scaffold. As such, it was decided to synthesis an example for which R_1 and R_3 would consist of simple phenyls, whilst R_2 remained a benzyl group.

After synthesis of the Weinreb amide **202**, this required addition with phenylethylene magnesium bromide. Unfortunately, this was significantly slower, giving a 33% yield with the rest of the material remaining as starting material. Pleasingly, the Michael addition with diethylamine and following pyrazole formation remained high yielding at 100% and 83% respectively. The alkylation again proved slow, with poor conversion giving rise to only a 27% yield. For this scaffold, the final step also gave a poor 20% yield as a result of unexpected ketone reduction, but a pleasing >20:1 diastereoselectivity.

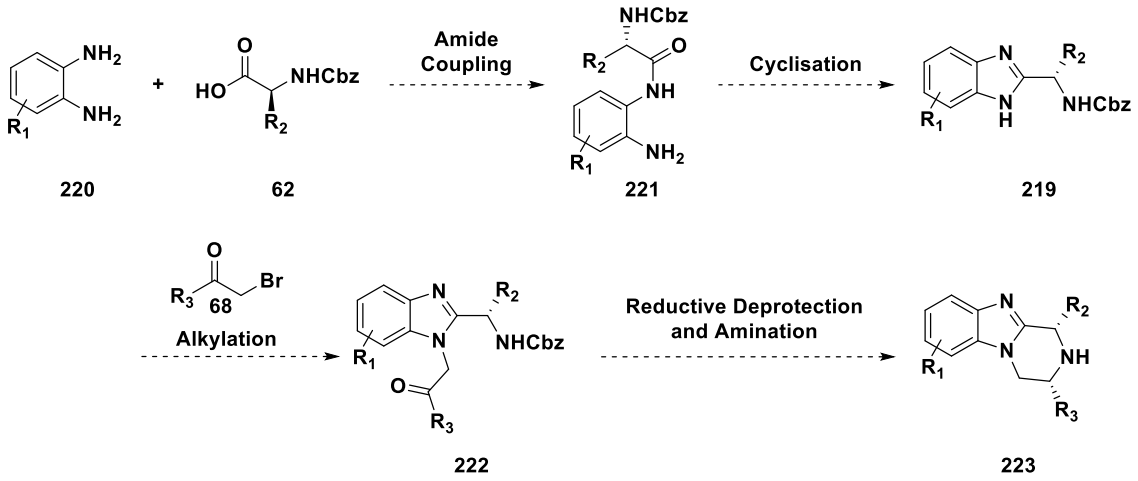


Scheme 3.27: Synthesis of an example of an pyrazole-based scaffold, with R_1 = Ph, R_2 = Bn, R_3 = Ph, ***218****: a.* ***49*** *(1.0 eq.), HNMeOMe.HCl (1.5 eq.), HOBt (1.1 eq.), HBTU (1.1 eq.) DIPEA (2.6 eq.), CH_2Cl_2, 12h, rt, 100%* ***202****; b.* ***202*** *(1.0 eq.), phenylethylene magnesium bromide (4.5 eq.), THF, 12h, -78 °C to rt, 33%* ***214****; c.* ***214*** *(1.0 eq.), $HNEt_2$ (1.1 eq.), CH_2Cl_2, 12h, rt, 100%* ***215****; d.* ***215*** *(1.0 eq.), $N_2HN_2H{\cdot}H_2O$ (1.1 eq.), HCl (aq) (1.1 eq.), 3h, reflux, 83%* ***216****; e.* ***216*** *(1.0 eq.), 2-bromoacetophenone* ***55*** *(1.2 eq.), DIPEA (1.0 eq.), THF, 12h, rt, 51%* ***217****; f.* ***217*** *(1.0 eq.), $NH_4{\cdot}CO_2H$ (30 eq.), $Pd(OH_2)/C$ (20 mol%), CH_3OH:H_2O (3:1 v/v), 12h, rt, 20%, >20:1 d.r.* ***218****.*

3.1.4.3. Benzimidazole

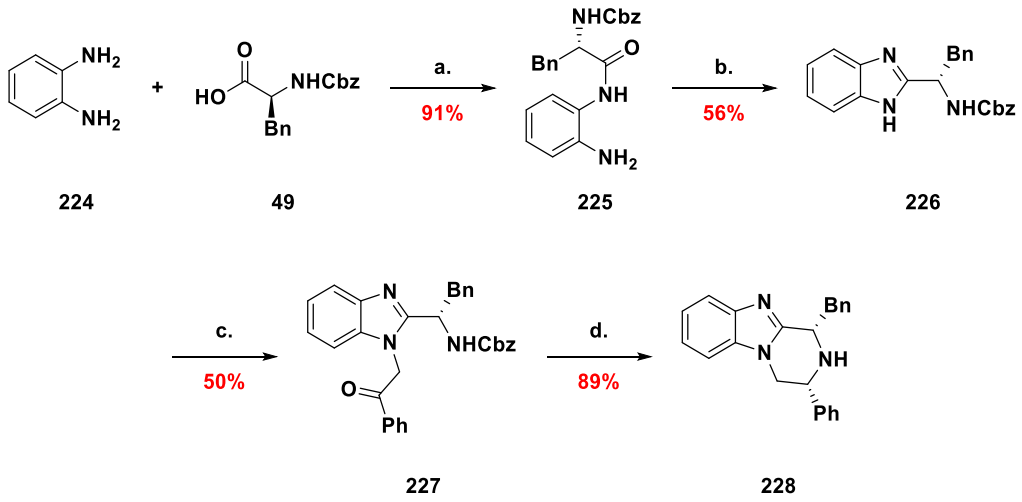
With the successful application of the designed route to three different heterocycles, such that the effect of the position and number of nitrogens in the 5-membered heterocycle could be explored, it was hoped that it would be simple to grow the 5-membered heterocycle into a bicycle, enabling the potential for further π-π interactions to be exploited.

The synthesis of scaffold **219** has excellent precedent in the literature,[262–267] and, furthermore, multiple examples were found with a range of substituents on the phenyl ring of the benzimidazole. Whilst the example described herein utilises the basic scaffold, we hoped that the functional groups explored in section 3.1.2 would, by analogy, be stable on this ring. The route identified first entailed an amide coupling between a phenyldiamine **220** and the carboxybenzyl-protected amino acid **62**. Heating in acid would thus present the required heterocycle **219** in preparation for the alkylation and subsequent reductive deprotection and amination (Scheme 3.28).



Scheme 3.28: Proposed synthetic route towards benzimidazole-based scaffolds.

The amide coupling proceeded smoothly using HATU to yield amide **225** in an excellent 91% yield. Following this, heating in acetic acid for two hours garnered the required benzimidazole scaffold **226** in a moderate 56% yield, ready for the alkylation. This step proved more difficult, with the reaction failing to go to completion, and therefore presenting only a 50% yield; however, this was a pleasing 83% based on recovered starting material. The final reductive deprotection and amination continued to perform well, with an excellent 89% yield and >20:1 diastereoselectivity.

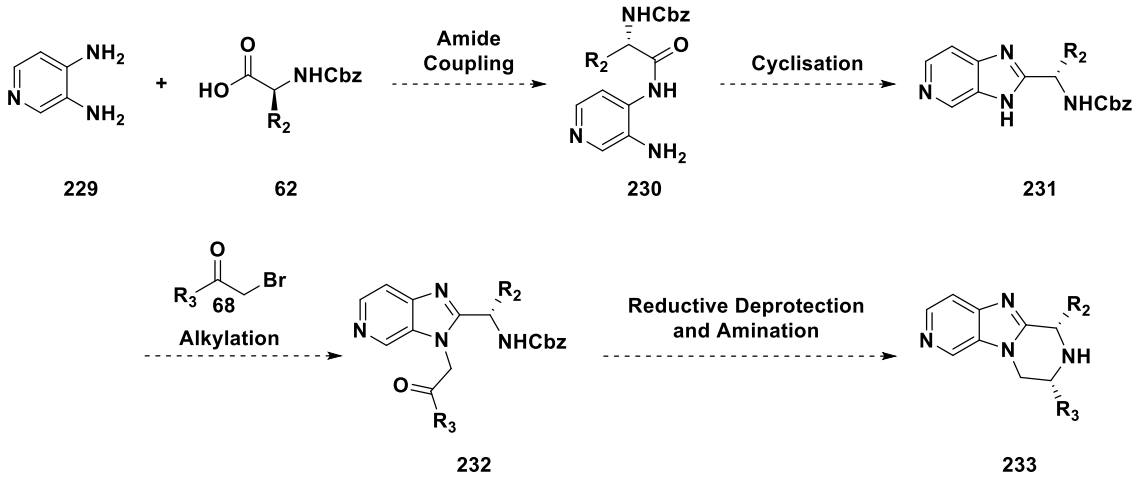


Scheme 3.29: Synthesis of an example of an benzimidazole-based scaffold, with R_2 = Bn, R_3 = Ph, ***228****: a. Cbz-L-phenylalanine* ***49*** *(1.0 eq.), o-phenylenediamine* ***224*** *(1.5 eq.), HATU (1.1 eq.), DIPEA (1.1 eq.), CH_2Cl_2, 12h, rt, 91%* ***225****; b.* ***225*** *(1.0 eq.), AcOH (0.6 M), 2h, 40 °C, 56%* ***226****; c.* ***226*** *(1.0 eq.), 2-bromoacetophenone* ***55*** *(1.2 eq.), K_2CO_3 (1.0 eq.), 12h, rt, 50%* ***227****; d.* ***227*** *(1.0 eq.), $NH_4{\cdot}CO_2H$ (30 eq.), $Pd(OH_2)/C$ (20 mol%), CH_3OH:H_2O (3:1 v/v), 12h, rt, 89%, >20:1 d.r.* ***228****.*

3.1.4.4. Imidazo[4,5-c]pyridine

A strategy within structure-activity relationship (SAR) explorations is to carry out a heteroatom or functional group "walk".[268] To anticipate this, it was hoped that the inclusion of an imidazo[4,5-c]pyridine-based scaffold into the library would illustrate the efficient manner in which such walks could be carried out through this synthetic route. It was hoped that the replacement of the phenyl ring in benzimidazole with a pyridyl ring would not prohibit the same amide coupling and acid catalysed route used for the construction of the benzimidazole scaffold, and satisfyingly, a literature example was found in which this chemistry was applied to the construction of an imidazo[4,5-c]pyridine.[269]

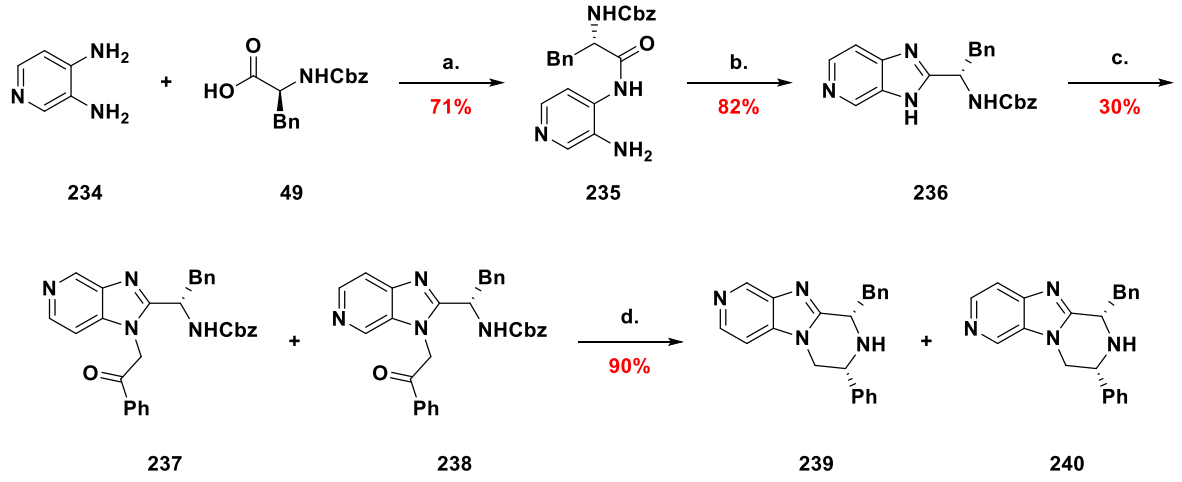
As such, the route proposed for the benzimidazole scaffold was applied to the imidazopyridine scaffold (Scheme 3.30). Starting with the amide coupling, this time between the carboxybenzyl-protected amino acids **62** and the relevant diaminopyridine **229**, the acid-catalysed cyclisation then bore the imidazopyridine scaffold **231** in preparation for alkylation. It was considered highly probable that, under the basic conditions required for alkylation, there would be tautomerisation between the two imidazo-nitrogen atoms. Whilst this was without doubt also occurring during the synthesis of the benzimidazole scaffold, the symmetry of the compound made it irrelevant. This would not be the case for the imidazopyridine scaffold; however, under a SAR-exploration point of view, this could be turned to our advantage, since two different nitrogen positions could be explored as the product of a single reaction, and all four positions through only two reactions. Thus, the final step could be carried out either on a mixture of the isomers, or on the individual isomers if they were found to be separable.



Scheme 3.30: Proposed synthetic route towards imidazopyridine-based scaffolds.

As with benzimidazole, although a variety of substituents would be compatible with the reaction conditions, the simplest example was synthesised (Scheme 3.31). Beginning with the amide coupling of 3,4-diaminopyridine **234** and Cbz-*L*-phenylalanine **49**, which achieved amide **235** in 71% yield. The

acid-catalysed cyclisation proceeded quantitatively to produce **236** in preparation for the alkylation. As previously discussed, this yielded both possible alkylation products **237** & **238**, in a 1:1 ratio, which proved to be inseparable by column chromatography, to give a combined yield of 30%. Whilst a more sensitive purification technique such as high pressure liquid chromatography (HPLC) could be used to separate them, the screening techniques proposed for this library would remain compatible with a mixture of known isomers, which could be separated at a later stage, in the case of the mixture proving to deliver a hit. Therefore, the mixture was carried forward to the final reductive deprotection and amination, delivering cyclised isomers **239** & **240** in an excellent 90% yield.

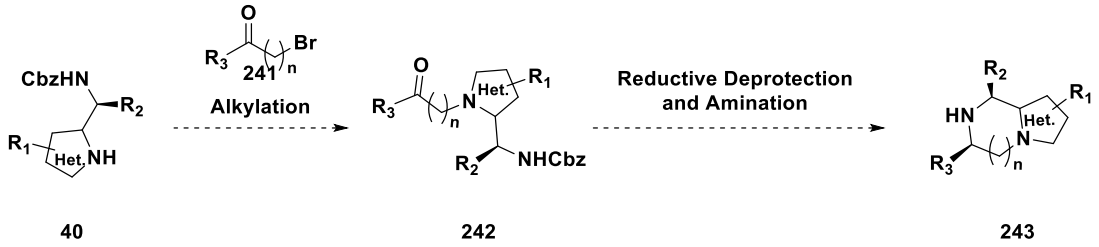


Scheme 3.31: Synthesis of an example of an imidazopyridine-based scaffold, with R_2 = Bn, R_3 = Ph, ***240****: a. Cbz-L-phenylalanine* ***49*** *(1.0 eq.), 3,4-diaminopyridine* ***234*** *(1.5 eq.), HATU (1.1 eq.), DIPEA (1.1 eq.), CH_2Cl_2, 12h, rt, 71%* ***235****; b.* ***235*** *(1.0 eq.), AcOH (0.6 M), 2h, 40 °C, 82%* ***236****; c.* ***236*** *(1.0 eq.), 2-bromoacetophenone* ***55*** *(1.2 eq.), K_2CO_3 (1.0 eq.), 12h, rt 30%,* ***237*** *&* ***238****; d.* ***237*** *&* ***238*** *(1.0 eq.), $NH_4{\cdot}CO_2H$ (30 eq.), $Pd(OH_2)/C$ (20 mol%), CH_3OH:H_2O (3:1 v/v), 12h, rt, 90%, >20:1 d.r.* ***239*** *&* ***240****.*

3.1.5. Studies towards Larger Saturated Rings.

Thus far, it has been demonstrated that the modular route designed for rapid library synthesis or SAR upon hit identification can be applied for significant variations in the size and nature of the 5-membered heterocyclic part of the scaffold, as well as the nature of the substituents in all three positions.

When considering the modulation of more challenging drug targets, such as PPIs, it has been found that larger, more flexible rings are advantageous, since in these cases shallower pockets, with fewer and more spatially separated hotspots for interactions, are being targeted. Thus it was hoped that another aspect of the scaffold which could be harnessed for diversification was the 6-membered partially saturated ring. The logical approach to tackling this challenge was to consider alkylating the heterocycle **40** with longer alkyl chains, such as a β-haloketone (yielding a 7-membered ring), or a γ-haloketone (yielding an 8-membered ring), with the final conditions unchanged (Scheme 3.32).

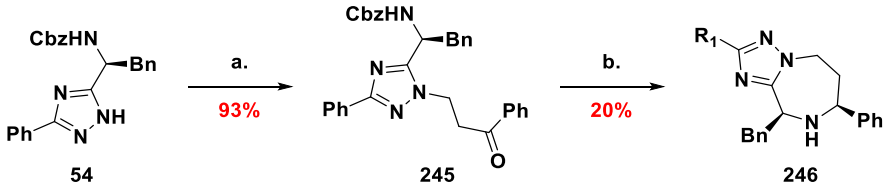


Scheme 3.32: Proposed Route to larger saturated rings.

The advantage of this approach would be its modular nature, in which the size of the saturated rings could be varied in two steps from the common intermediate **40**, enabling rapid SAR. However, when considering the alkylation of **40**, longer chains would be less reactive to S_N2, without the carbonyl in a position to lower the energy of the lowest unoccupied molecular orbital and thus the transition state. In the event that the alkylation could be carried out successfully, the cyclisation would be significantly less favourable than for the 6-membered ring due to larger rings being less thermodynamically stable,[270] and with the increased flexibility of the rings, there was some concern that the diastereoselectivity would be reduced.

With these concerns in mind, the synthesis of an example of both the 7- and 8-membered scaffolds was attempted, with the triazole ring, and the previously used phenyl and benzyl substituents. Pleasingly, the 7-membered ring proved to be extremely successful (Scheme 3.33). Alkylation was carried out smoothly using 3-chloropropiophenone **244**, and **245** was isolated in 93% yield. The additional concern for the alkylation using β-bromoketones had been the risk of simply eliminating the chlorine under basic conditions, and therefore seeing no evidence of alkylation if subsequent conjugate addition did not take place. Pleasingly, no indication of this was observed The final reductive deprotection and amination also proved to be fruitful, with the final scaffold isolated in a poor 20% yield and >20:1

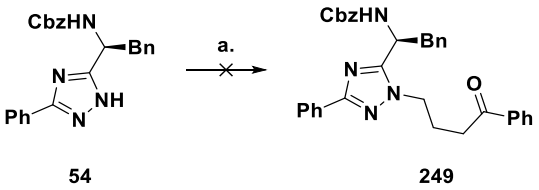
diastereoselectivity, demonstrating the strong natural bias of these scaffolds for the *cis*-diastereomeric product. Although this was low yielding, with the remaining material found to be side product from the reduction of the ketone, we were pleased to achieve sufficient material for testing.



Scheme 3.33: Synthesis of an example of an triazole-based scaffold with a7-membered saturated ring, with R_1 = Ph, R_2 = Bn, R_3 = Ph, ***246****: a.* ***54*** *(1.0 eq.), 3-chloropropiophenone* ***244*** *(1.2 eq.), K_2CO_3 (1.0 eq.), 12h, rt, 93%* ***245****; b.* ***245*** *(1.0 eq.), $NH_4{\cdot}CO_2H$ (30 eq.), $Pd(OH_2)/C$ (20 mol%), $CH_3OH:H_2O$ (3:1 v/v), 12h, rt, 86%, >20:1 d.r.* ***246****.*

Following on from this success, it was hoped that it could be replicated for the 8-membered ring. Unfortunately, the alkylation conditions used throughout this project for the alkylation step, were insufficient for an alkylation with 4-chlorobutyrophenone **247** (Table 3.13, Entry 1). A literature search suggested the addition of catalytic sodium iodide might improve the reactivity, with the iodide first displacing the chloride, before the desired S_N2 reaction can take place (Table 3.13, Entry 2). With the iodide much easier to displace with its lower charge density making it significantly more stable in organic solvents. Despite stirring overnight, this remained as starting material **54**. In the hope of driving the reaction forward, it was subjected to microwave heating at 120 °C, using the same conditions but with the solvent switched from acetone to the less volatile dimethoxyethane (Table 3.13, Entry 3). Once again, only starting material remained. Finally, the 4-iodobutyrophenone was used, but unfortunately no product was formed (Table 3.13, Entry 4).

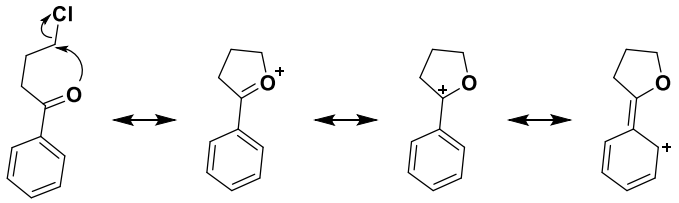
*Table 3.13: Optimisation of conditions for alkylation with γ-haloketones: **54** (1.0 eq.), 4-halobutyrophenone **248** (1.0 eq.), conditions in table.*



54 **249**

Entry	Halo	Conditions	Yield (%)	Outcome
1	Cl	K_2CO_3 (1.2 eq.), Acetone, 12h, rt	0	Starting Material, **54**
2	Cl	K_2CO_3 (1.2 eq.), NaI (0.1 eq.), Acetone, 12h, rt	0	Starting Material, **54**
3	Cl	K_2CO_3 (1.2 eq.), KI (0.1 eq.), DME, 1h mw, 120 °C,	0	Starting Material, **54**
4	I	K_2CO_3 (1.2 eq.), acetone, 12h, reflux	0	Starting Material, **54**

A paper from Karachev and Popkov suggested that two problems contribute to this lack of reactivity:[271] (i) the expected inactivity of the chlorine at the γ-position relative to the carbonyl; (ii) the formation of the stable intermediate phenyltetrahydrofuran carbocation **250**, as first suggested in 1956 (Scheme 3.34).[271,272]

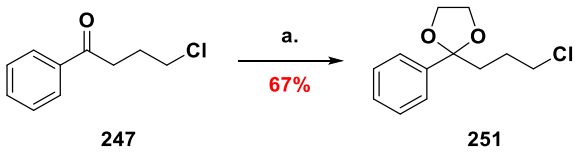


250

Scheme 3.34: Proposed route for the formation of the intermediate stable phenyltetrahydrofuran carbocation 250 prohibiting the alkylation reaction.[271]

The solution to this, proposed by the author of the aforementioned study, was to protect the ketone, prior to the alkylation step, such that formation of **250** would be prohibited,[271] leaving the poorly reactive γ-chlorine as the only challenge. The advantage of this route is that the carbonyl can be unveiled simply through an acidic work-up, without the need for a separate deprotection step. To this end, 2-(3-chloropropyl)-2-phenyl-1,3-dioxolane **251** was prepared, in which the carbonyl group was protected as an acetal (Scheme 3.35). This was achieved by refluxing 4-chlorobutyrophenone **247** in ethylene glycol,

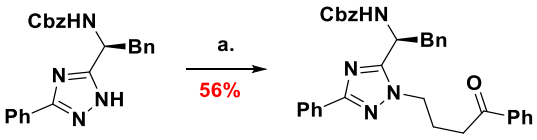
with trifluorosulphonic acid as a catalyst and triethylorthoformate, in a moderate yield, providing sufficient material for exploring the alkylation conditions further.



247 251

Scheme 3.35: Synthesis of 2-(3-chloropropyl)-2-phenyl-1,3-dioxolane, ***251****: a. 4-chlorobutyrophenone* ***247*** *(1.0 eq.), trifluoromethane sulfonic acid (0.01 eq.), triethylorthoformate (1.5 eq.), ethylene glycol (1.5 eq.), 12h, reflux, 67%* ***251****.*

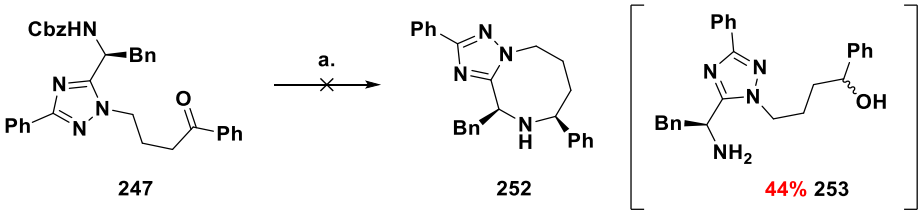
Pleasingly, alkylation proceeded smoothly once the ketone had been protected, with deprotection occurring during the work-up, such that the alkylated triazole was achieved in a moderate 56%.



54 249

Scheme 3.36: Alkylation of triazole ***54*** *with 2-(3-chloropropyl)-2-phenyl-1,3-dioxolane,* ***251****: a.* ***54*** *(1.0 eq.), 2-(3-chloropropyl)-2-phenyl-1,3-dioxolane* ***251*** *(1.2 eq.),* K_2CO_3 *(1.0 eq.) AcCN (0.2 M), 12h, reflux, 56%* ***249****.*

With the successfully alkylated triazole **249** in hand, all that remained was to test whether the saturated 8-membered ring **252** could be achieved using the palladium dihydroxide catalysed reductive deprotection and amination. Regrettably, the desired cyclised scaffold was not achieved, and instead the alcohol **253** was isolated in a 44% yield.



247 252

Scheme 3.37: Attempted formation of the 5,8-triazole-based scaffold: a. 247 (1.0 eq.), $NH_4{\cdot}CO_2H$ *(30 eq.),* $Pd(OH_2)/C$ *(20 mol%),* $CH_3OH{:}H_2O$ *(3:1 v/v), 12h, rt, 0%* ***252,*** *44%* ***253****.*

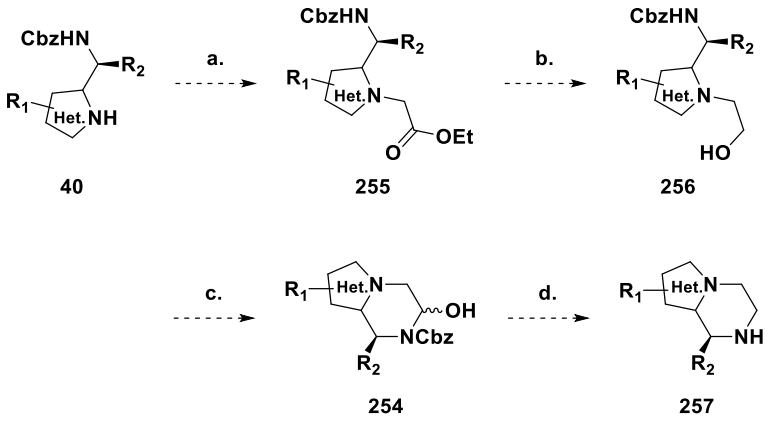
3.2. Studies towards Achieving Single Chiral Centres

The ease with which these scaffolds can be achieved offers excellent opportunities for rapid SAR in terms of both the stereochemistry and functionalities at this position. However, within drug discovery, small pockets are often targeted, for which the compounds thus far synthesised have the potential to be too large. One way of circumventing this issue, beyond choosing smaller functional groups, would be to limit the saturated ring to a single chiral centre. It was hoped that the synthetic route proposed could be simply adapted to allow for the synthesis of scaffolds with a single substituent in both of the positions accessed.

3.2.1. Single Substitution in the R_2-Position

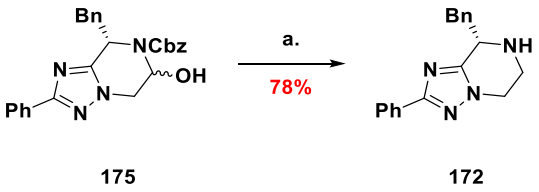
For the R_2 position, when exploring methods for reducing the hemiaminal **175** to the imine **169** (Section 3.1.3), it was serendipitously identified that the palladium dihydroxide conditions used for the reductive deprotection and amination sequence could be used on this scaffold to carry out concomitant deprotection and hemiaminal reduction to generate amine **172**.

To this end, it was proposed that single enantiomers with a chiral centre in the R_2 position of the scaffolds could be generated *via* hemiaminal **254** from the heterocyclic scaffolds **40** (Scheme 3.38).



Scheme 3.38: General route to access enantiomerically pure heterocyclic scaffolds with a single substituent in the saturated ring in the R_2 position: a. ***40*** *(1.0 eq.), ethyl-2-bromoacetate (1.2 eq.), K_2CO_3 (1.0 eq.), 12h, rt,* ***255****; b.* ***255****(1.0 eq.), $LiBH_4$ (1.2 eq.), Et_2O, 3h, 0 °C to rt,* ***256****; c.* ***256*** *(1.0 eq.), IBX (3.0 eq.), EtOAc (0.1 M), 12h, reflux,* ***254****; d.* ***254*** *(1.0 eq.), $NH_4{\cdot}CO_2H$ (30 eq.), $Pd(OH_2)/C$ (20 mol%), CH_3OH:H_2O (3:1 v/v), 12h, rt,* ***257****.*

Amine **172** was synthesised from hemiaminal **175** in an excellent 78% yield (Scheme 3.39). One key feature of our methodology is the mildness of the conditions employed throughout the synthetic sequence, which would avoid epimerisation of the sensitive stereogenic centre. Enantiospecificty of the process was confirmed by analysis of the corresponding Moscher amide.

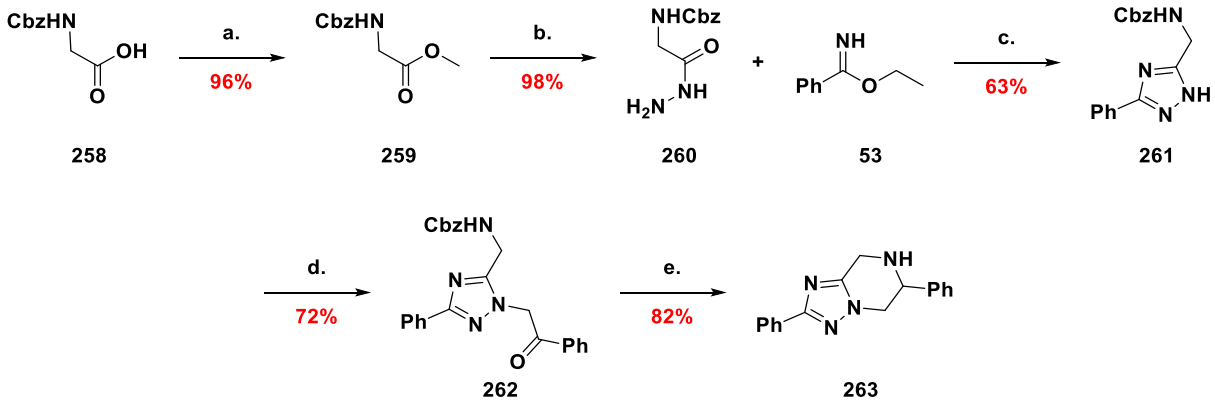


Scheme 3.39: Formation of a scaffold with a single chiral centre in the R_2 position: a. ***175*** *(1.0 eq.), $NH_4{\cdot}CO_2H$ (30 eq.), $Pd(OH_2)/C$ (20 mol%), $CH_3OH{:}H_2O$ (3:1 v/v), 12h, rt, 78%* ***172****.*

Thus for the purposes of SAR, a full library of compounds could be formed, with the availability of enantiopure amino acids being the only restriction onto the functionalities accessible in the R_2 position *via* the following developed route.

3.2.2. In the R_3-position

It was hoped that by repeating the synthesis of the desired scaffold with glycine, such that the R_2 position would be unsubstituted, would enable a single chiral centre to be generated in the R_3 position of the saturated ring. To this end, the initial synthesis was repeated with glycine **258** (Scheme 3.40). Its conversion to the corresponding amino hydrazide *via* the ester proceeded smoothly, with a yield of 94% over the two steps on a multi-gram scale. The cyclisation gave triazole **261** in a moderate 63%, followed by alkylation in a good 72% yield. The final reductive deprotection and amination progressed with an excellent 82% yield to give the racemic scaffold.



Scheme 3.40: Synthesis of a scaffold with a single chiral centre at the R_3 position: a. Cbz-L-phenylalanine ***258*** *(1.0 eq.), $SOCl_2$ (1.4 eq.), CH_3OH, 3h, rt, 96%* ***259****; b.* ***259*** *(1.0 eq.), $NH_2NH_2{\cdot}H_2O$ (5 eq.), CH_3OH, 12h, rt, 98%* ***260****; c.* ***260*** *(1.0 eq.),* ***53*** *(1.2 eq.), EtOH, 6h, reflux, ii. AcOH, 2h, reflux, 63%* ***261****; d.* ***261*** *(1.0 eq.), 2-bromoacetophenone* ***55*** *(1.2 eq.) K_2CO_3 (1.0 eq.), acetone, 12h, rt, 72%* ***262****; e.* ***262*** *(1.0 eq.), $NH_4{\cdot}CO_2H$ (10 eq.), $Pd(OH_2)/C$ (20 mol%), $CH_3OH{:}H_2O$ (3:1 v/v), 82%* ***263****.*

For the purposes of initial screening it is unimportant that a racemic compound has been generated, however, upon the identification of a hit, it would become necessary to ascertain the biologically active

enantiomer prior to further optimisation. To that end, although we have yet to follow through on this chemistry, there is significant literature precedent for the enantioselective reductive amination step, most commonly using rhodium, ruthenium or iridium catalysis.[273–276]

3.3. Computational Analysis

As previously discussed, assessing the chemical diversity of a compound library is important for determining the potential for its success in drug discovery.[277] Two common approaches are used to display the degree of diversity exhibited by compound libraries: "principle moments of inertia" analysis (PMI) and "principal component analysis" (PCA).

To assess the three-dimensional shape diversity of a compound library, the individual constituents' moments of inertia along three mutually orthogonal principle axes are calculated and plotted as normalised PMI ratios on the triangular PMI plot. This plot therefore provides a visual demonstration of how one-, two- and three-dimensional the molecular scaffolds are, which corresponds to how rod-like, disk-like or sphere-like they are.[277]

Multiple chemical "descriptors" can be used to describe compounds and, combined, these can be used to visualise each compound in a library as a single point in chemical space. PCA reduces these multi-dimensional descriptors into two-dimensional vectors that can be plotted on a scatter plot. Whilst this is advantageous as it combines information from multiple descriptors, these are chosen by the operator and therefore are subject to human bias; also important to note is that any changes to the descriptors could drastically change the form of the scatter plot.[62]

Computational analysis of the compounds synthesised in this thesis was performed using Molecular Operating Environment (MOE) software package version 2012.10 from the Chemical Computing Group. A detailed procedure of the PMI analysis and PCA is given in Section 7.1.

3.3.1. Principal Moments of Inertia (PMI) Analysis

An initial conformational search and energy minimisation on the library of compounds synthesised in this thesis was carried out, and the lowest energy conformation for each compound selected (see appendix 7.1.2) Principal moments of inertia were calculated for these lowest energy conformations, as well as for 40 top-selling drugs and 1,000 Maybridge fragment library members, so that we could compare the shape diversity between these collections and our library (full details of the PMI analysis can be found appendices 7.1.1. and 7.1.2.). The PMI plot produced is shown below (Figure 3.6).

The aim of this project was to develop a synthetic route towards libraries of compounds with increased complexity when compared to two-dimensional molecules, but not to extend too far into three-dimensional space where the increased complexity has the potential to drastically decrease the hit rate. The line parallel to the axis between rod-like and disk-like represents the edge of what can be considered three-dimensional space. It is pleasing to see that most compounds in our library lie around this line,

without clustering together. Hence they demonstrate good diversity on the cusp of three-dimensionality. Compared to the Maybridge fragment library, for which a large proportion of the compounds lie flush with the two-dimensional axis, this demonstrates the improved molecular complexity achieved in this work. Whilst this work in general demonstrates less three-dimensionality than the known drugs plotted, this merely illustrates the scope for molecular expansion during the optimisation process from hit to lead.

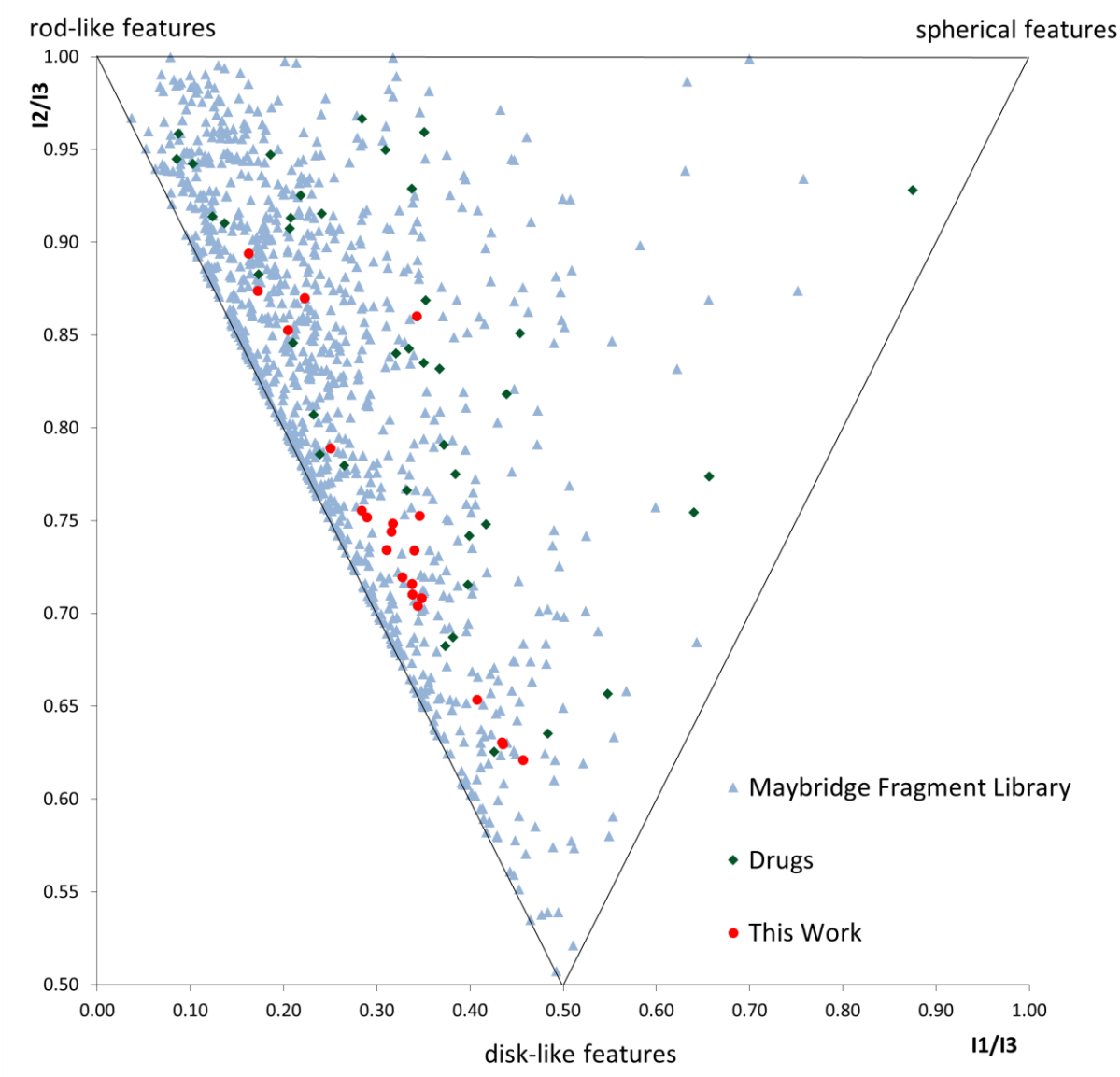


Figure 3.6: Principle moments of inertia plot illustrating the shape diversity of our compound library and the 2 reference sets. The red markers represent our library.

3.3.2. Principal Component Analysis (PCA)

PCA was carried out using 17 molecular descriptors which covered a broad range of 17 physicochemical and structural properties, such as molecule flexibility (KierFlex), partition coefficient between octanol and water (Slog P), topological polar surface area (TPSA) and number of hydrogen bond donors (a_don) (For full list see appendix 7.1.3, Table 7.2). These 17 descriptors were then combined to construct 17 new unit-less axes called "principal components", each of which has contributions from each of the original descriptors. These 17-dimensional vectors were linearly transformed into two-dimensional vectors, calculated so as to represent as much of the variance in the database as possible and sorted by their contribution to the variance. The first six principle components were found to be responsible for over 95% of the variance exhibited by the library, with the first three principle components representing over 85% of the total variance (Table 3.14). As such, the first three components were deemed sufficient to construct the PCA plots (Figure 3.7).

Table 3.14: Contribution of each principal component to the total library variance.

PC Number	Deviation	Condition	% Variance
1	3.245	1.000	61.929
2	1.624	3.994	77.436
3	1.308	6.158	87.493
4	0.943	11.831	92.727
5	0.590	30.263	94.774
6	0.494	43.108	96.210

These PCA plots illustrate that the chemical space spanned by this work overlaps to some extent with that of synthetic drugs, but considerably less so with that of natural products. Furthermore, our library occupies some regions of the graph barely populated by the two reference sets, highlighting the potential for exploring under-exploited regions of chemical space.

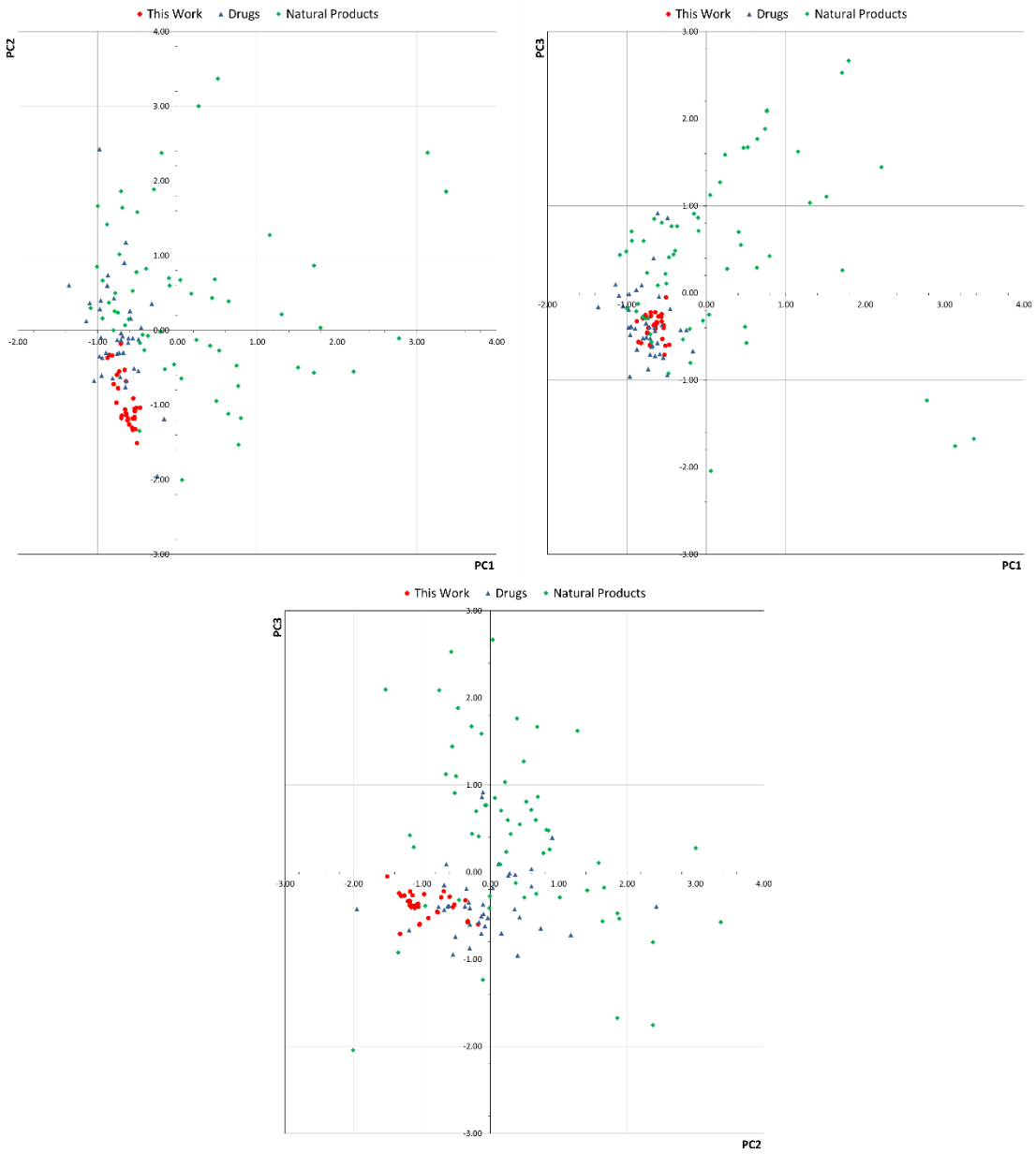


Figure 3.7: PCA plots of this work and 2 reference libraries: a. PC1 versus PC2; b. PC1 versus PC3; c. PC2 versus PC3. This work (red dots), 40 synthetic drugs (blue triangles) 60 natural products (green rhombus). See appendix 7.1.1 for the three libraries.

When considering the contributions of the 17 descriptors (Table 3.15) we can see those properties which gave the most significant contributions towards the variance in each principle component. When considering PC1, there are 11 descriptors with significant contributions, suggesting that the library exhibits some degree of diversity in each of these properties.

Table 3.15: Component loadings of the 17 descriptors to the first six principal components, with the top contributing parameters to each principal component highlighted in blue, with darker blue indicating a greater contribution. The values were normalised automatically by the MOE software. For definitions of descriptors see appendix 7.1.3.

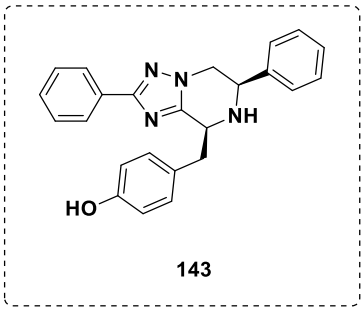
	PCA 1	PCA 2	PCA 3	PCA 4	PCA 5	PCA 6
a_acc	0.0182	0.0126	0.0197	0.0508	-0.0688	0.1204
a_aro	-0.0001	-0.0296	-0.0373	0.0164	-0.0054	0.0924
a_don	0.0224	0.0271	-0.0424	0.0270	-0.1334	0.2482
a_nN	0.0169	-0.0172	-0.1056	-0.0541	-0.2050	-0.1804
a_nO	0.0150	0.0166	0.0214	0.0306	0.0653	-0.0151
ASA_H	0.0003	-0.0009	0.0009	-0.0009	-0.0019	0.0002
ASA_P	0.0006	0.0010	-0.0008	0.0016	0.0047	-0.0026
b_rotN	0.0102	0.0036	-0.0141	-0.0623	0.1198	0.1262
chiral	0.0127	0.0136	0.0482	0.0550	-0.0670	0.0629
KierFlex	0.0130	0.0050	0.0155	-0.0386	-0.0111	-0.0083
logS	-0.0221	0.0872	-0.0157	0.0699	-0.1448	0.1092
mr	0.0113	-0.0106	0.0036	-0.0095	-0.0074	-0.0391
rings	0.0153	-0.1268	-0.0266	0.3202	0.1988	-0.1211
SlogP	-0.0103	-0.0668	0.0841	-0.0276	-0.0218	0.1199
TPSA	0.0007	0.0007	-0.0009	0.0005	-0.0001	-0.0004
Weight	0.0003	-0.0002	0.0001	-0.0001	0.0001	-0.0010
vol	0.0003	0.0002	0.0002	-0.0003	-0.0004	-0.0010

3.4. Screening

3.4.1. High-Throughput X-ray Crystallography Screening

The Diamond light source (DLS) synchrotron in Oxfordshire (UK) has developed the XChem screening facility at the beamline 104-1 for the high throughput X-ray crystallographic screening of fragment libraries. They use the ECHO acoustic liquid handler to soak target crystals with solutions of the fragments in singleton format, allowing 1,000 individual soaks to be carried out efficiently and accurately in less than 10 minutes.[278] Crystal harvesting is semi-automated through the use of a microscope and x-y stage shifter such that approximately 100 crystals per hour can be harvested. The X-ray diffraction data collection is fully automated, enabling the screening of almost 700 crystals within 24 hours, and PanDDA software enables efficient processing of multiple data sets for the detection and modelling of bound fragments.[279]

The facility has established collaborations within both academia and industry all over the world: more recently, this has extended to the Spring group. The principle aim behind this collaboration was to enable the routine screening of the multiple DOS libraries developed within the group against novel biological targets provided by both internal and external users of the facility. From one such screening campaign conducted in 2017, one of the library members was identified by Joe McLoughlin from the Hyvönen Group, Cambridge as a weak binder of the protein Activin A (Figure 3.8).



143

*Figure 3.8: Compound **143** was identified as a weak binder for Activin A.*

The initial screening was carried out using 4% PEG300 within the soaking solution (Figure 3.9). When the compound was soaked under different conditions, without the PEG, no binding was seen, suggesting compound **143** was an extremely weak binder. PEG is often used in soaking solutions since it can act as a solubilising agent for poorly soluble compounds.[280] Therefore, this result might also be attributable to the low solubility of compound **143** in the PEG-free conditions used. Given that another compound in a different DOS library from the Spring group was found to be a stronger binder, no follow up work was carried out on this initial hit. However, we hope future hits against novel biological targets might be identified through this collaboration.

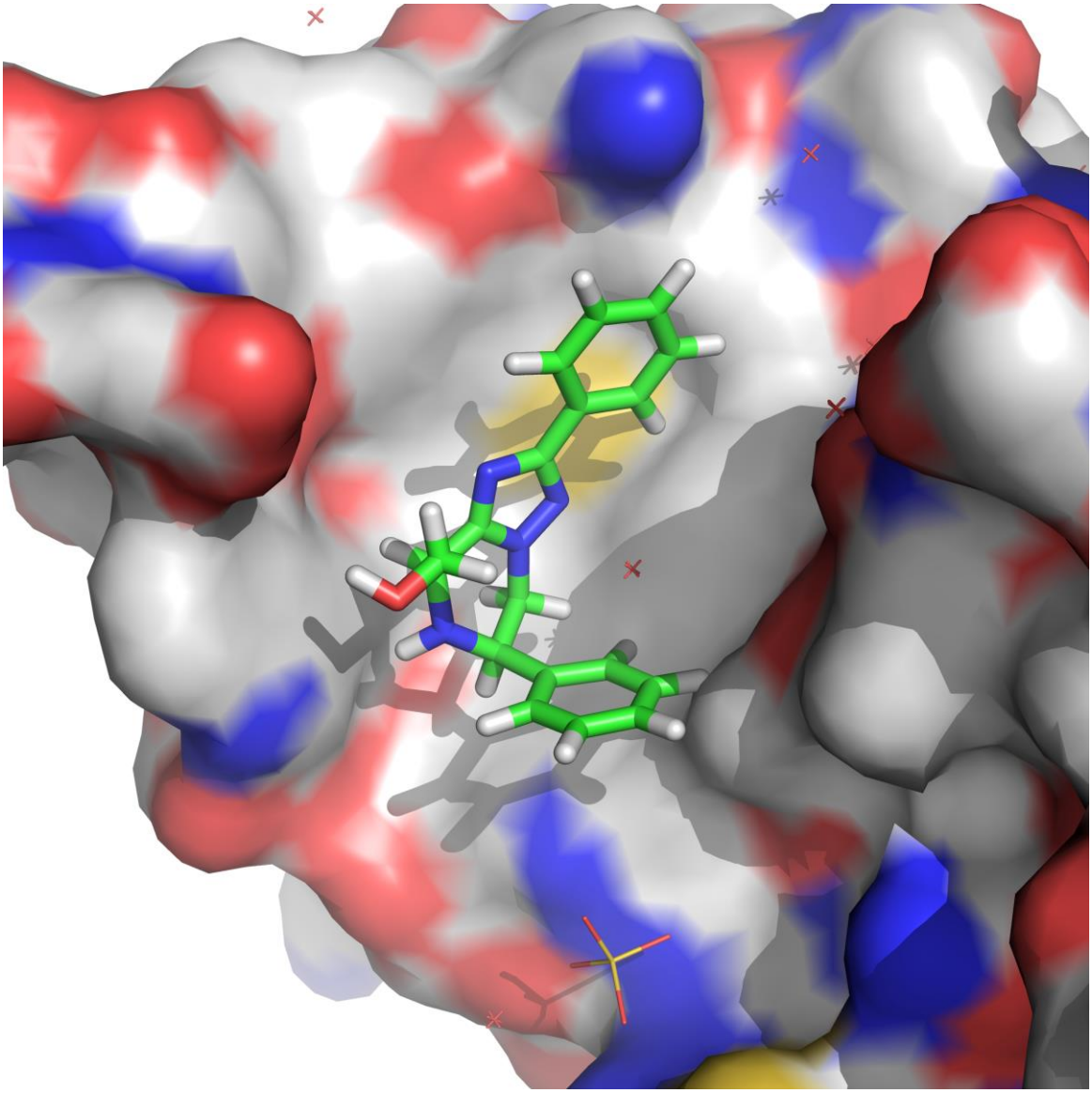


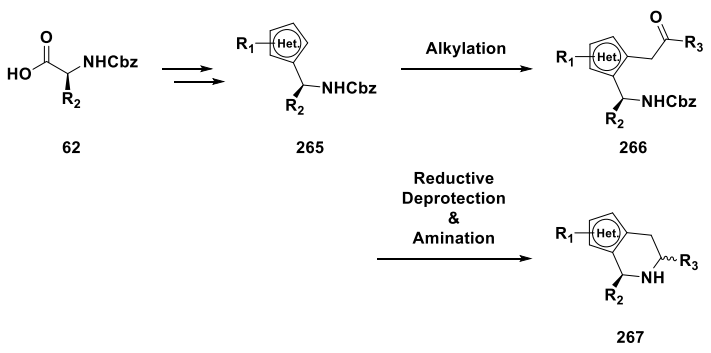
*Figure 3.9: Crystal Structure of compound **143** bound to Activin A. Image provided by Joe McLoughlin, Hyvönen Group, Cambridge.*

4. Conclusions and Future Work

4.1. Conclusions

This work aims to improve aspects of the current significant decline in the pharmaceutical industry, which is seen in the decreased number of approvals of NCEs, the lower quality of R&D pipelines and the reduction of revenue generated. We believe this can be attributed to the lack of diversity and poor quality of existing screening libraries. Library compounds should be diverse but also synthetically tractable and incorporate synthetic handles for growth such that chemical optimisation *via* SAR studies can be carried out effectively and efficiently. The synthesis of screening libraries through robust and tolerant synthetic strategies should aim to generate diverse libraries targeting novel scaffolds which incorporate the desired polar functional groups and synthetic handles in a step-efficient manner. In particular, there is a significant need for novel bicyclic heteroaromatic scaffolds within libraries, since these are not only under-represented in existing libraries, but are extremely useful in drug discovery due to their limited flexibility and ability to form important binding interactions.

The development of a modular, divergent and step-efficient diastereoselective synthetic route for the synthesis of partially saturated bicyclic heteroaromatic scaffolds has been carried out in order to address this (Scheme 4.1). A particular focus of this was the incorporation of functional handles that could provide growth vectors for fragment or lead elaboration, and as such, the conditions developed are tolerant to a wide range of functional groups, such as alcohol, trifluoromethyl and amino functionalities. In addition, to enable rapid hit validation and optimisation, synthesis requires just 4-6 steps from commercially available starting materials. The use of amino acids is a key aspect of this work as they provide a large pool of inexpensive and commercially available starting materials, but significantly the chiral centre was essential for generating the diastereoselectivity during the reductive deprotection and amination step.



Scheme 4.1: Final synthetic route developed.

The initial work was carried out on a triazole-based scaffold for a 5,6-bicyclic system; however, this was later extended to other heterocycles and larger saturated rings, such that the overall library created

has 7 different scaffolds and 24 members. Furthermore, adaptations allow access to structures with a single chiral centre in either the R_2- or R_3-position, in which, the stereochemistry in the R_2-position is predetermined by that of the starting amino acid, whilst currently in the R_3-position synthesis is carried out racemically (Figure 4.1).

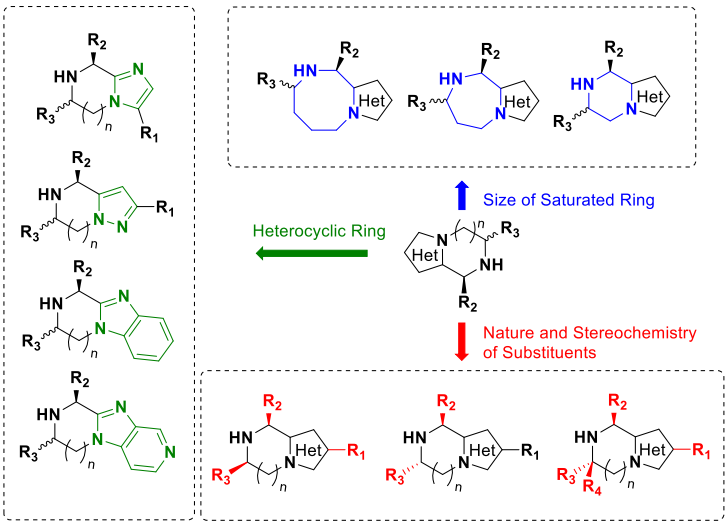


Figure 4.1: Illustration of the scope for the synthesis of diverse scaffolds.

Computational analysis determined that the library demonstrated enhanced sp^3 character (Figure 3.6) and increased chirality compared to typical fragment libraries (Table 4.1). Since this work foccussed on developing a robust methodology for the synthesis of these scaffolds, phenyl rings were used as unreactive "place-holders" during the exploration of the scope of the synthetic strategy. As a result, when considering the physicochemical properties of the library generated (Table 4.1), the SlogP, molecular weight and number of aromatic rings lie well outside of the desirable range for fragment-based drug discovery and lead-oriented synthesis. Pleasingly, the polar surface area and numbers of hydrogen bond donors, hydrogen bond acceptors rotatable bonds and chiral centres lie-close to, if not within these guidelines. Therefore, although the library itself does not comply to the drug discovery physicochemical property guidelines, the synthetic route designed has the potential to be applied to the construction of fragment-like, lead-like or drug-like compound libraries through careful selection of the substituents, heterocycle and the size of the saturated ring. Furthermore, whilst the library of compounds generated do not comply to the constraints of fragment-based drug discovery, some of the library members have been incorporated into Diamond's XChem crystallography screening, and from this a hit was identified for Activin A.

Table 4.1: Comparison of some of the physicochemical properties of the compound library generated by this work, with the typical ranges with fragment-like,[107] lead-like[281] and drug-like[103] compound libraries.

Property	This library	Fragment Library	Lead-like Library	Drug-like Library
SlogP	-5.26	0 - 2	-1 - 3	≤ 5
Molecular Weight	359	140 - 230	200 - 350	≤ 500
Polar Surface Area (PSA)	45.2	≤ 60	-	≤ 75
Hydrogen Bond Acceptors (HBA)	3.00	≤ 3	≤ 9	≤ 10
Hydrogen Bond Donors (HBD)	1.08	≤ 3	≤ 5	≤ 5
Rotatable Bond Count (RBC)	3.92	≤ 3	≤ 10	≤ 10
Chiral centres	1.90	0 - 2	1-2	-
Aromatic rings	3.68	-	≤ 3	-

Given the necessity of developing new approaches for the step-efficient synthesis of diverse screening libraries, this work offers a highly efficient and adaptable route to highly sought after partially saturated heteroaromatic scaffolds.

4.2. Future Work

This work has focussed on testing the tolerance of this route to different functionalities, and the ways in which it can be adapted for the synthesis of diverse scaffolds. However it has the potential to generate a library of millions of compounds based around multiple scaffolds.

4.2.1. Expansion of the Chemistry

To date, this work has extended the proposed synthetic route to the synthesis of 7 different heterocycle-based scaffolds and 2 different saturated ring sizes. Furthermore, it has accessed a single enantiomer at the R_2-position and a single chiral centre racemically in the R_3-position.

Future synthetic work on this project would focus on expanding the heterocycles that could be accessed. In addition, potentially even larger saturated heterocycles could be targeted, or different heteroatom-based saturated rings (Figure 4.2). Finally, accessing substitutions in the remaining position on the piperazine ring.

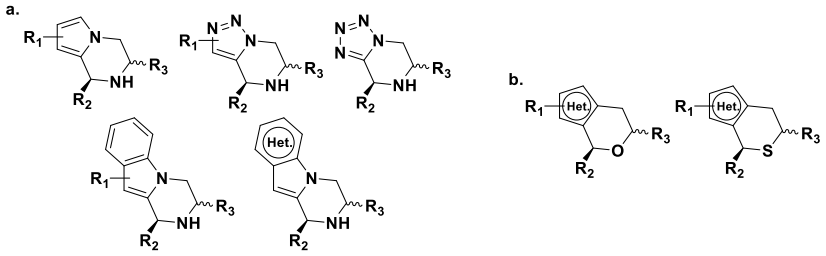


Figure 4.2: Examples of other potential scaffolds a. heterocyclic-based scaffolds which could be targeted; b. potential heteroatom variation within the saturated ring.

An important area which requires further investigation is that of accessing single enantiomers for a single chiral centre at the R_3-position.

4.2.2. Illustrating the Biological Relevance

The biological relevance of these semi-saturated bicyclic heteroaromatic scaffolds was illustrated by their presence in phase II clinical trial candidate, KAF 156 and an FDA approved drug, Januvia©, with KAF 156 containing an imidazole-based scaffold and Januvia© (Sitagliptin) a triazole-based scaffold. Despite the presence of these semi-saturated bicyclic heteroaromatic scaffolds in approved drugs and compounds in the clinic, limitations in their current synthetic routes prevents easy exploration of SAR

and investigation of certain substitution patterns and stereoselectivities; however, by utilising this new methodology we hope that further biological applications can easily and efficiently be identified.

4.2.2.1. KAF 156

KAF 156 is awaiting the start of phase III clinical trials for treatment against the *Plasmodium falciparum* and *Plasmodium vivax* forms of the malaria parasite. A total of 5,000 hits (all < 1.25 □M) were initially identified through a screening campaign on a library of approximately 2 million compounds using a cell-based proliferation assay of *Plasmodium falciparum*.[282] From these initial five-thousand hits and after multiple rounds of SAR during the lead optimisation process the final clinical candidate KAF156 was identified (Figure 4.3).[131,132]

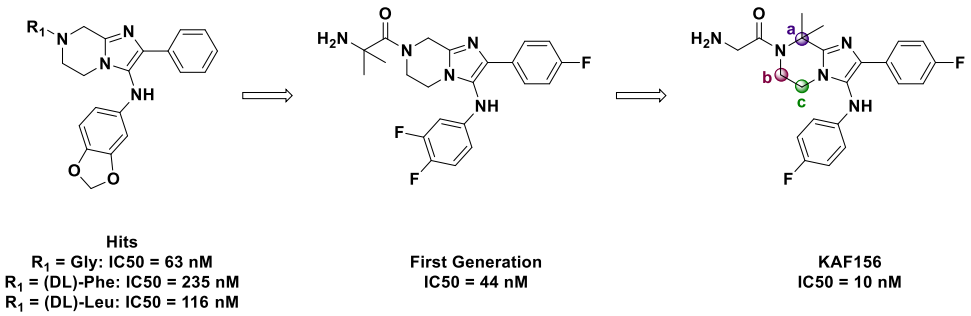
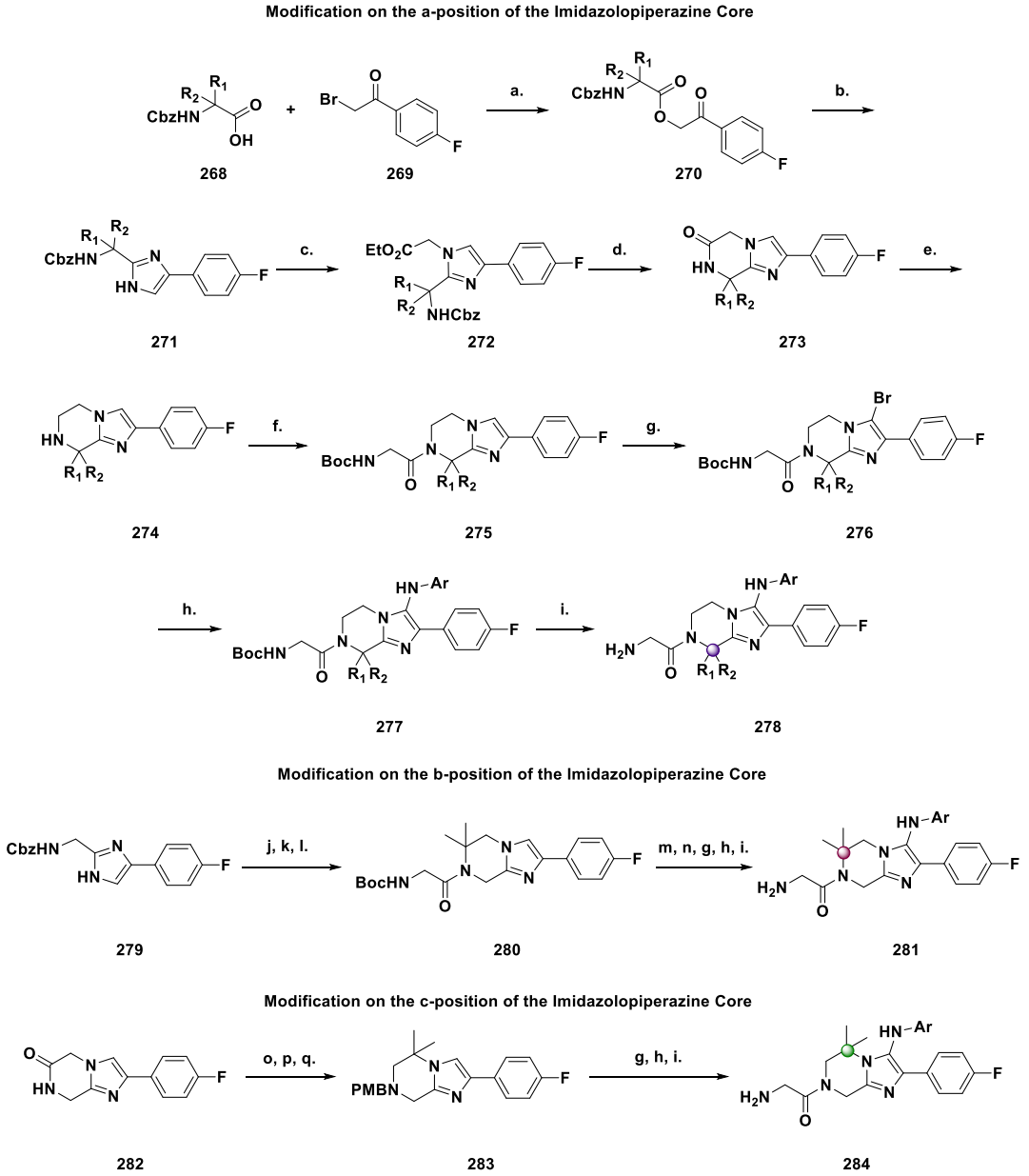


Figure 4.3: KAF156 developed by Novartis: a, b and c illustrate the positions at which substitution patterns were explored for SAR studies.

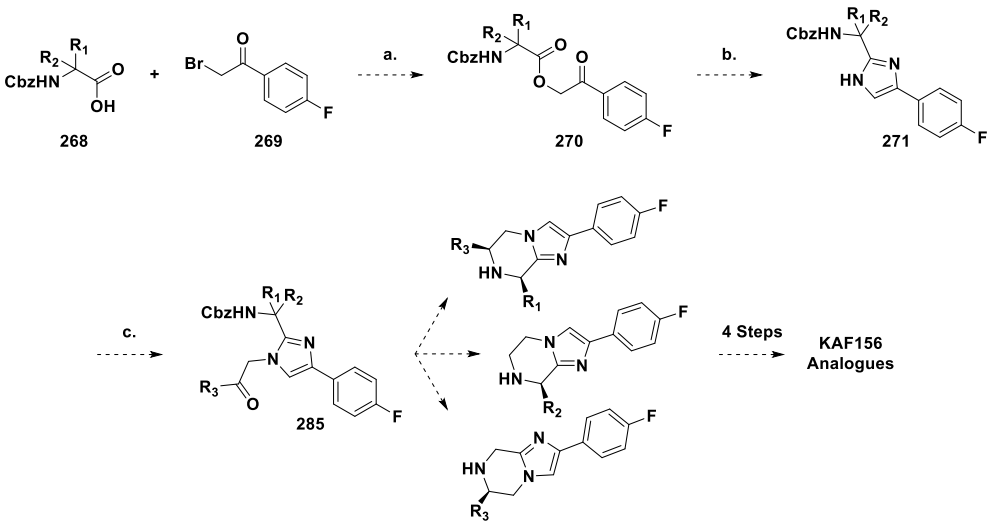
We believe this lead optimisation process could have been streamlined through the use of a more modular synthetic route to the imidazolopiperazine scaffolds which formed the main pharmacophore. In particular, when considering the chemistry carried out (Scheme 4.2), a separate route was required in order to explore substitution in the three available positions of the piperazine ring (Figure 4.3, positions a, b and c). At positions b and c**,** only double substitutions were possible, and at no point were multiple positions in the ring substituted simultaneously. Furthermore, it was only possible to stereoselectively control the substitution at position a through the use of chiral amino acid starting materials.



Scheme 4.2: The synthetic route used for the SAR studies carried out in the lead optimisation of second-generation antimalarial agents:[132] *a. K_2CO_3, DMF, rt, 84% **270**; b. NH_4OAC, toluene, reflux, 88% **271**; c. ethyl 2-bromoacetate, Cs_2CO_3, DMF, rt, 83% **272**; d. Pd/C, H_2 (1 atm), CH_3OH, rt, 91%, **273**; e. BH_3·THF, THF, reflux, 95%, **274**; f. N-Boc-glycine, HATU, DIPEA, CH_2Cl_2, rt, 70%, **275**; g. Br_2, AcOH, CH_2Cl_2, rt, 100% **276**, 55% **(281)**, 80% **(284)**; h. $ArNH_2$, $Pd_2(dba)_3$, xantphos, Cs_2CO_3, dioxane, 150 °C, 89% **277**; i. TFA, CH_2Cl_2, rt, 52% **278**, 55% (2 steps) **281**, 46% (2 steps) **284**; j. methallyl chloride, K_2CO_3, KI, DMF, rt, 55%; k. AcOH/MsOH (6:1), 210 °C, 39%; l. N-Boc-glycine, HATU, DIPEA, DMF, rt, 57% **280**; m. TFA, 70 °C, quantitative; n. N-Boc-glycine, HATU, TEA, DMF, rt, 49% **(281)**; o. PMBCl, KOH, DMF, 0 °C to rt, 63%; p. MeI, NaH, DMF, rt, 86%; q. BH_3·THF, THF, reflux, 100% **283**.*

When considering the application of the modular route described within this thesis (Scheme 4.3), whilst the stereo-control at position a is also achieved through the chiral amino acid starting materials, it offers the possibility of introducing substitution at positions a and b simultaneously and diastereoselectively. Furthermore, it would be possible to access single substitutions in positions a and b stereoselectively.

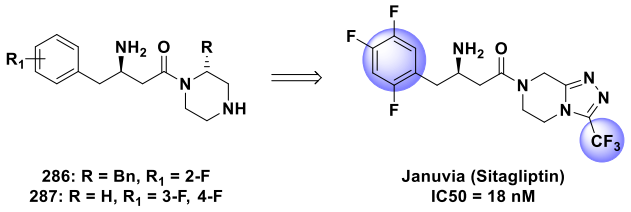
This route could therefore be used to access previously unexplored substitution patterns, as well as improving the efficiency of the synthesis of the compounds used for the SAR studies during the development of KAF 156



Scheme 4.3: Scheme illustrating how the modular synthetic route for the synthesis of partially saturated bicyclic heteroaromatics could be applied to the rapid and step-efficient synthesis of analogues of KAF 156: a. ***268****,* ***269****, K_2CO_3, DMF, rt; b.* ***270****, NH_4OAC, toluene, reflux; c.* ***271****, α-bromoketone, K_2CO_3, acetone, rt.*

4.2.2.2. Januvia©

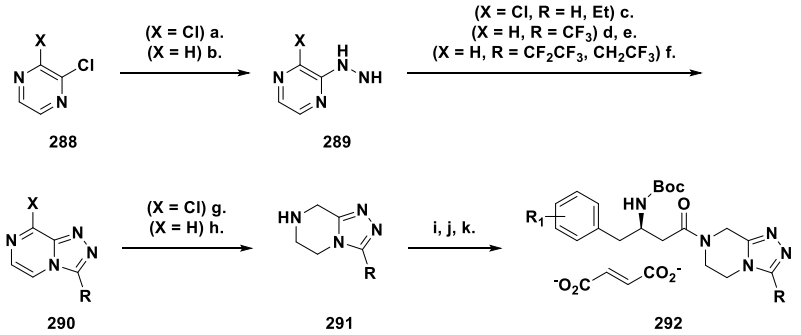
Januvia© was FDA approved in 2006 for the treatment of type II diabetes through the inhibition of DPP-IV. It was developed from a *β*-amino acid-based structure which had high DPP-IV inhibitory potency but poor pharmacokinetic properties due to the metabolism of the heterocycle moiety (Scheme 4.4).[135] As a result, a study was carried out to replace the problematic piperazine ring with a more robust heterocycle, such as a fused heterocyclic system.



Scheme 4.4: Optimisation of novel β-amino acid based potent inhibitors ***286*** *and* ***287*** *of DPP-IV to improve the pharmacokinetic properties and metabolic stability lead to the development of Januvia.© Figure adapted from reference.*[135]

The initial SAR studies carried out revolved only around the substituent on the triazole ring and the substituents around the left hand phenyl ring (both highlighted blue, Scheme 4.4), possibly due to the synthetic challenges involved with regio- and stereo-selectively substituting the piperazine ring. The synthetic route began from a pyrazine ring, onto which the triazole ring was built (Scheme 4.5).

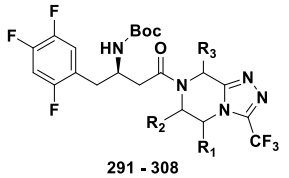
Selective reduction of the 6-membered ring then gave the partially saturated scaffold. Hence, any substituents incorporated at the pyrazine stage would give a racemic mixture upon reduction, and late-stage substitution would be challenging to control.



Scheme 4.5: Initial synthetic route used to synthesize analogues for the SAR studies which resulted in the identification of Januvia© as a clinical candidate for the treatment of type II diabetes:[135] *a. $NH_2NH_2{\cdot}H_2O$, EtOH, reflux; b. $NH_2NH_2{\cdot}H_2O$, 120 °C, 45 mins; c. $CH(OCH_3)_3$ or $C_2H_5C(OC_2H_5)_3$, reflux; d. $(CF_3CO)_2O$, 0 °C to rt; e. PPA, 140 °C, 18 h; f. $CF_3CF_2CO_2H$ or $CF_3CH_2CO_2H$; g. PtO_2, CH_3OH, H_2; h. H_2, 10% Pd/C, EtOH; i. β-amino acid, HOBT, EDC, DIPEA, DMF, rt, 18 h; j. Saturated HCl, CH_3OH; k. i. 1N, NaOH, EtOAc, ii. Fumaric acid, EtOH, rt*

Whilst Januvia© proved to be sufficiently potent without substituting the piperazine ring, a number of SAR studies have since been carried out focussing on different regions of the compounds. In particular, a study was carried out exploring the alkyl substitution around the triazolopiperazine moiety (Table 4.2). The key challenge here was that multiple routes were required in order to access the various substitution positions, and furthermore almost all compound were synthesised racemically and the resultant diastereomers separated upon coupling to the enantiopure β-amino acid moiety, resulting in poor isolated yields throughout.

Table 4.2: The various Januvia© analogues synthesised through the SAR studies.[134]



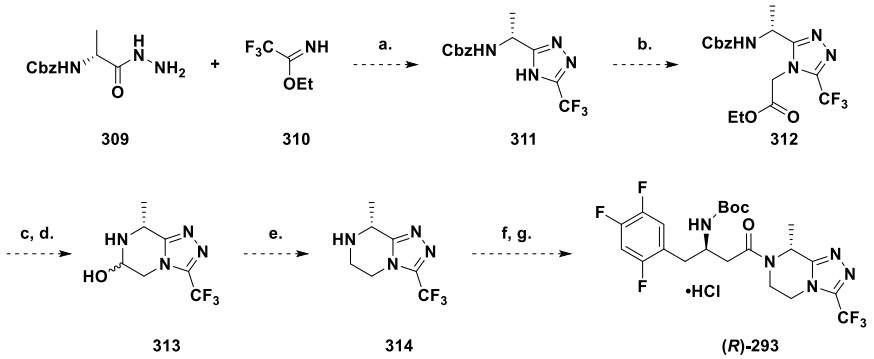
291 - 308

	R_1	R_2	R_3	DPP-4 IC_{50} (nM)
291	Me[b]	H	H	(*S*)-23; (*R*)-14
292	H	Me[a,b]	H	(*S*)-91; (*R*)-42
293	H	H	Me[a,b]	(*S*)-88; (*R*)-4.3
294	Me, Me	H	H	92
295	H	H	Me, Me	175
296	Me	H	Me	100, 209, 12, 11
297	H	H	Et[a,b]	113, 5.0
298	H	H	CH_2CF_3[a,b]	123, 5.7
299	H	H	CH_2CHCH_2[a,b]	1.5, 32
300	H	H	$CH_2CON(CH_3)_2$[a,b]	377, 2.8
301	H	H	CH_2Ph[a,b]	140, 0.66
302	H	H	CH_2(4-methoxyphenyl)[a,b]	320, 0.43
303	H	H	CH_2(2-trifluoromethylphenyl)[a,b]	438, 0.31
304	H	H	CH_2(2-fluorophenyl)[a,b]	131, 0.46
305	H	H	CH_2(4-fluorophenyl)[a,b]	116, 0.18
306	H	H	CH(OH)(4-fluorophenyl)[a,b]	430, 0.32, 90, 0.50
307	H	H	CH_2(3,5-*bis*-trifluoromethylphenyl)[a,b]	587, 6.3
308	H	H	CH_2(2-pyridyl)[a,b]	132, 0.40

[a] R_1 and R_3 S/R isomers synthesised in a single reaction and separated by flash column chromatography. [b]Stereochemistry of the diasterioisomers unknown; order of the IC_{50} values corresponds with the elution order. Based on X-ray structure determination of the analogue with $R_1 = R_2 = H$, $R_3 = CH_2$(4-fluorophenyl), slower eluting isomers were tentatively assigned as (R)-isomers

Application of the work described within this thesis to the synthesis of various Januvia© analogues would have significantly improved the stereoselectivity, efficiency and yields. In particular, substitution at the R_3 position with (*R*)-stereochemistry was found to be of critical importance for superior potency, leading to the identification of compound **(*R*)-293** which was found to have a 4-fold increase in DPP-IV activity over Januvia© and which we consider could be more efficiently and economically

synthesised *via* this route (Scheme 4.6). Unfortunately, the compound was found to have intolerable side-effects in *in vivo* studies and was therefore taken no further.



Scheme 4.6: Proposed step-efficient and stereo-selective synthesis of an improved DPP-IV inhibitor with high selectivity, a good pharmacokinetic profile and in vivo efficacy: a. i. EtOH, reflux, 3h, ii. AcOH, reflux, 2h; b. Ethyl bromoacetate, K_2CO_3, acetone, rt, 12h; c. $LiBH_4$, CH_2Cl_2, -78 °C to rt, 12h; d. IBX, EtOAc, reflux, 12h; e. $NH_4{\cdot}CO_2H$ (30 eq.), $Pd(OH_2)/C$ (20 mol%), $CH_3OH:H_2O$ (3:1 v/v), 12h, rt; f. β-amino acid, HOAT, HATU, DIPEA, DMF, rt, 18 g. satd. HCL/CH_3OH.

Work to synthesise analogues *via* the synthetic route described within this thesis is currently being carried out.

4.2.3. Biological screening

4.2.3.1. High-throughput X-ray Crystallography Screening

Thus far, a proportion of the library synthesised in this work has been incorporated in the Diamond XChem crystallography screening library, and we hope this will continue to generate hits against novel targets. From these hits, synthesis of closely related analogues will be required for hit validation and optimisation, and this will be a simple and efficient process as a result of the forethought given in the design of the synthetic route to the scaffolds.

4.2.3.2. In Silico Screening

In silico screening is a well-established computational technique for the prediction of biological targets of compounds on the basis of chemical structure by using information from known bioactivity information.[283] These predictions can then be validated experimentally afterwards. There are two commonly used approaches:[284]

1) Structure-based methods exploit the available structural information on the protein and scoring functions to predict ligand-target pairs;

2) Ligand-based methods use similarity searching on known ligand-target pairs available from chemogenomic databases, relying on the theory that the similar features between compounds are responsible for the target binding.

Traditionally, these techniques have been used to identify the mode of action of molecules identified as biologically active through phenotypic screening. However, similarity matches from *in silico* screening can also be used to direct biological screening towards particular, more likely target classes. The Bender group have developed a target prediction protocol called PIDGIN which makes use of, not only known activity data, but also inactivity data, to give a more well-rounded analysis of the probability of activity.[284] Our collaboration with the Bender group presents the possibility of analysing this work with PIDGIN, and using the resulting data to explore future phenotypic or target-based screening campaigns.

4.2.3.3. Other Screening Aims

In addition, given the opportunity, we would like to be able to include our library in the phenotypic or target-based screening campaigns. This would not only further validate the choice of scaffold as biologically relevant, but could potentially identify novel and synthetically tractable hits for challenging new targets.

4.2.4. The Virtual Library and its Potential

The work here has attempted to efficiently illustrate the broad applicability of the synthetic route designed. However, it has the potential, even within the constraints of those scaffolds already explored of generating almost 2 million different compounds (Table 4.3). Without a doubt, synthesising all possible combinations is an impossible task; however, with the ever increasing development and success of in-silico screening, we propose that the virtual library this generates based on commercially available starting materials could be screened in-silico, and only those compounds which demonstrate good potential for biological activity could be later synthesised and screened. Furthermore, it would be possible to synthesise the 1,454 fragments possible, a significantly more achievable goal, highlighting the advantages of this drug discovery strategy.

Table 4.3: Table demonstrating the number of different commercially available starting materials for each of the scaffolds explored in this work from Sigma Aldrich. The total possible scaffolds for each heterocycle therefore incorporates cis- and trans-diastereomers, as well as single substitutions on the piperazine ring in the R_2 and R_3 positions. [a.] Includes both enantiomers of each available natural and synthetic amino acid.

Heterocycle	Substituents		R_3		Total Possible scaffolds	Fragment Scaffolds
	R_1	**R_2**	**6-Membered**	**7-Membered**		
Triazole	31	78	74	7	430,683	484
Imidazole	10	78	74	7	138,930	397
Pyrazole	36	78	74	7	500,140	502
Benzimidazole	48	78	74	7	666,864	46
Imidazopyridine	9	78	74	7	125,037	25
				Total	1,861,654	1,454

5. Experimental Details

5.1. General experimental details

All non-aqueous reactions were performed in dry glassware under a stream of nitrogen using anhydrous solvents. Tetrahydrofuran was dried over sodium wire and distilled from a mixture of lithium aluminium hydride and calcium hydride with triphenylmethane as the indicator. Dichloromethane, toluene and methanol were all distilled from calcium hydride. Petroleum ether was distilled before use and refers to the fraction between 40-60 ^{o}C.

Chemicals were purchased from Sigma Aldrich and used as received unless otherwise stated.

Reactions were carried out at ambient temperature unless otherwise stated. All temperatures below 0 ^{o}C were achieved with an external bath: those of 0 ^{o}C were maintained using an ice/water bath, those of lower temperatures using a dry ice/ acetone bath. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated.

Where possible, reactions were monitored using TLC or liquid chromatography-mass spectrometry (LCMS). Analytical thin layer chromatography (TLC) was performed on commercially available glass pre-coated Merck Kiesel gel 60 F254 plates. Visualisation was achieved by quenching of UV fluorescence (λ_{max} = 254 nm) or by staining with potassium permanganate. R_f values are quoted to the nearest 0.01. LCMS was performed using a Waters ACQUITY H-Class UPLC with an ESCi Multi-Mode Ionisation Waters SQ Detector 2 Spectrometer using MassLynz 4.1 software.

Flash column chromatography was performed using slurry-packed SiO_2 (Merck Grade 9385, 230-400 mesh) under a positive pressure of N_2. Celite refers to AW Standard Cuper-Cel NF.

Optical rotations were recorded on an Anton Parr MCD 100 Polarimeter. $[\alpha]_D^{20}$ values are reported in 10^{-1} deg cm^2 g^{-1} at 589 nm, concentration (c) is given in g dL^{-1}.

Infrared spectra were recorded neat (unless otherwise stated) on a Perkin Elmer Spectrum One FT-IR spectrometer with internal referencing. Selected absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}) and are assigned as: weak (w), medium (m), strong (*S*) or broad (br).

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded using an internal deuterium lock at ambient probe temperatures (unless otherwise stated) on the following instruments: Bruker DPX-400 (400 MHz), Bruker Avance 400 QNP (400 MHz), Bruker BB 500 (500 MHz) and Bruker Avance 500 Cryo Ultrashield (500 MHz). Chemical shifts (δ_H) are referenced to the residual non-deuterated solvent peak and quoted in parts per million (ppm) to the nearest 0.01 ppm. Coupling constants are quoted in Hertz to the nearest 0.1 Hz. Data are reported in the format: chemical shift, integration, multiplicity

[app = apparent; br = broad; s =s singlet; d = doublet; t = triplet; q = quartet; quin = quintet; m = multiplet; or as a combination of these, e.g. dd], coupling constant(*S*), assignment. Proton assignments were determined either on the basis of unambiguous chemical shift, coupling patterns, by patterns observed in the two-dimensional experiments (^{1}H-^{1}H COSY, HMBC and HMQC) or by analogy to fully interpreted spectra for related compounds.

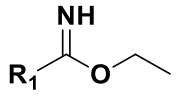
Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded by broadband proton spin decoupling at ambient probe temperatures (unless otherwise stated) using an internal deuterium lock on the following instruments: Bruker DPX-400 (100 MHz), Bruker Avance 400 QNP (100 MHz), Bruker BB 500 (125 MHz) and Bruker Avance 500 Cryo Ultrashield (125 MHz). Chemical shifts (δ_C) are referenced to the residual non-deuterated solvent peak and quoted in parts per million (ppm) to the nearest 0.1 ppm. Assignments are supported by either chemical shift, APT/DEPT, two dimensional experiments (HMBC and HMQC) or by analogy to fully interpreted spectra for related compounds.

The numbering of molecules for the assignment of ^{13}C and ^{1}H spectra does not follow the IUPAC naming system.

High resolution mass spectrometry (HRMS) measurements were carried out on a Micromass LCT Premier spectrometer using electron spray ionisation (ESI) techniques. Masses are quoted within the error limits of ±5ppm mass units.

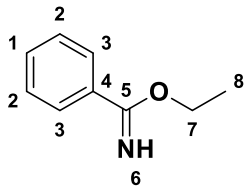
5.2. Efficient Synthesis of 1,2,4-Triazole heterocycles: *cis*-diastereomer

5.2.1. General procedure for the formation of Imidates



General Procedure 1: Acetyl chloride (8 eq.) was added dropwise over 15 minutes to a stirred solution of the required nitrile in ethanol (12 eq.). The mixture was stirred at room temperature overnight. The solution was cooled to 0 °C before the addition of saturated aqueous sodium hydrogen carbonate until the evolution of gas ceased. The solution was then warmed to room temperature and extracted with diethyl ether (3 x 150 mL). The combined organic fractions were washed with brine (50 mL) and dried ($MgSO_4$) before the solvent was removed under reduced pressure to yield the crude compound. The title compound was reacted on without further purification.

5.2.1.1. Ethylphenylcarbimidate (53)



Following General Procedure 1: benzonitrile **50** (5.00 mL, 48.5 mmol), acetyl chloride (27.6 mL, 388 mmol) and ethanol (34 mL, 582 mmol) were used to yield the title compound **53** as a yellow liquid (7.11 g, 47.7 mmol, 98%).

R_f = 0.66 (EtOAc)

IR ν_{max} = 3301 (w, N-H), 2980 (w, C-H), 1631 (s, C=N), 1578 (m, C=C)

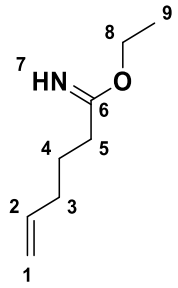
^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.74 (2H, d, *J* = 5.5 Hz, H3), 7.46-7.38 (3H, m, H1 & 2), 4.33 (2H, q, *J* = 6.8 Hz, H7), 1.42 (3H, t, *J* = 6.8 Hz, H8)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 167.9 (C5), 132.9 (C4), 130.7 (C1), 128.5 (C2), 126.6 (C3), 61.8 (C7), 14.2 (C8)

HRMS (ESI+): found $[M + H]^+$ 150.0915, $C_9H_{12}NO^+$ required 150.0919

This data is in accordance with that previously reported.[285]

5.2.1.2. Ethyl hex-5-enimidate (77)



Following General Procedure 1: 5-hexenenitrile **72** (0.910 mL, 8.00 mmol), acetyl chloride (4.55 mL, 64.0 mmol) and ethanol (5.60 mL, 96.0 mmol) were used the yield the title compound **77** as an orange liquid (1.13 g, 8.00 mmol, 100%).

R_f = 0.21 (20% EtOAc in hexane)

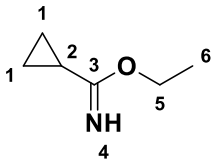
IR ν_{max} = 2936 (m, C-H), 1642 (s, C=N), 1537 (s, C=C)

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 11.45 (1H, s, H7), 5.75 (1H, ddt, *J* = 17.1, 10.3, 7.1 Hz, H2), 4.98 - 5.09 (2H, m, H1), 4.62 (2H, q, *J* = 6.9 Hz, H8), 2.73 (2H, t, *J* = 7.1 Hz, H5), 2.13 (2H, q, *J* = 7.1 Hz, H3), 1.83 (2H, quin, *J* = 7.1 Hz, H4), 1.47 (3H, t, *J* = 6.9 Hz, H9)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 179.1 (C6), 136.3 (C2), 116.3 (C1), 70.6 (C8), 32.6 (C3), 32.4 (C5), 24.8 (C4), 13.5 (C9)

This data is in accordance with that previously reported.[286]

5.2.1.3. Ethyl cyclopropanecarbimidate (78)



Following General Procedure 1: cyclopropanebenzonitrile **72** (2.80 mL, 38.1 mmol), acetyl chloride (12.2 mL, 171 mmol) and ethanol (27 mL) was used the yield the title compound as a white solid **78** (2.97 g, 26.2 mmol, 69%).

R_f = 0.14 (20 %EtOAc in hexane)

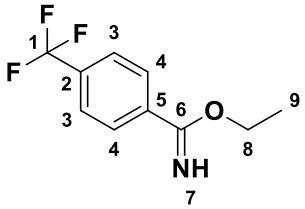
IR: ν_{max} = 2924 (m, C-H), 1636 (s, C=N),

^{1}H NMR (400 MHz, d_6DMSO): δ_H = 4.38 (2H, q, *J* = 7.0 Hz, H5), 2.19 (1H, tt, *J* = 7.8, 4.6 Hz, H2), 1.29 (3H, q, *J* = 7.1 Hz, 6), 1.10 - 1.23 (4H, m, H1)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 178.9 (C3), 68.6 (C5), 13.2 (C6), 12.3 (C2), 10.0 (C1)

This data is in accordance with that previously reported.[287]

5.2.1.4. Ethyl 4-(trifluoromethyl)benzimidate (79)



Following General Procedure 1: 4-(triflluoromethyl)benzonitrile **73** (123 mg, 0.73 mmol), acetyl chloride (0.40 mL, 5.70 mmol) and ethanol (0.5 mL) were used the yield the title compound **79** as a yellow liquid (127 mg, 0.58 mmol, 80%).

R_f = 0.27 (20% EtOAc in hexane)

IR ν_{max} = 3366 (m, N-H), 3048 (m, C-H), 1653 (s, C=N), 1624 (s, C=C), 1577 (m, C=C)

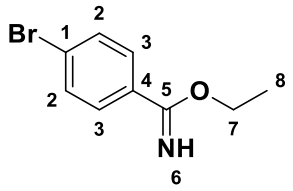
^{1}H NMR (400 MHz, d_6-DMSO): δ_H = 8.31 (2H, d, *J* = 8.2 Hz, H3), 8.02 (2H, d, *J* = 8.2 Hz, H4), 4.65 (2H, q, *J* = 7.0 Hz, H8), 1.49 (3H, t, *J* = 7.0 Hz, H9)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 169.8 (C6), 131.3 (C2), 130.4 (C5), 128.8 (C4), 126.4 (C3), 115.6 (C1), 69.9 (C8), 13.9 (C9)

HRMS (ESI+): found $[M + H]^+$218.0798, $C_{10}H_{11}F_3NO^+$ required 218.0793

This data is in accordance with that previously reported.[288]

5.2.1.5. Ethyl 4-bromobenzimidate (80)



Following General Procedure 1: 4-bromobenzonitrile **74** (130 mg, 0.73 mmol), acetyl chloride (0.40 mL, 5.70 mmol) and ethanol (0.5 mL) were used the yield the title compound **80** as a yellow liquid (110 mg, 0.48 mmol, 66%) Yield calculated from NMR

R_f = 0.27 (20 %EtOAc in hexane)

IR ν_{max} = 3403 (s, N-H), 3199 (m, C-H), 1656 (s, C=N), 1621 (s, C=C), 1589 (m, C=C)

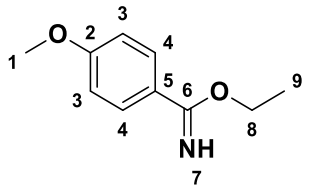
^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.22 (2H, d, *J* = 8.4 Hz, H2), 7.65 (2H, d, *J* = 8.4 Hz, H3), 4.89 (2H, q, *J* = 6.4 Hz, H7), 1.57 (1H, t, *J* = 6.4 Hz, H8)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 170.2 (C5), 132.6 (C2), 131.3 (C4), 131.0 (C3), 124.1 (C1), 71.6 (C7), 13.8 (C8)

HRMS (ESI+): found $[M + H]^+$ 228.0027, $C_9H_{11}BrNO^+$ required 228.0024

This data is in accordance with that previously reported.[289]

5.2.1.6. Ethyl 4-methoxybenzimidate (81)



Following General Procedure 1: 4-methoxybenzonitrile **75** (1.06 g, 8.00 mmol), acetyl chloride (4.55 mL, 64.0 mmol) and ethanol (5.6 mL, 96.0 mmol) were used the yield the title compound **81** as an orange liquid (1.28 g, 7.14 mmol, 89%).

R_f = 0.84 (EtOAc)

IR ν_{max} = 2980 (m, C-H), 1630 (s, C=N), 1607 (s, C=C), 1512 (m, C=C)

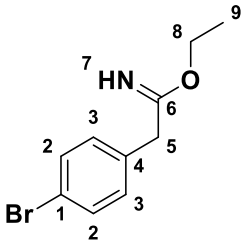
^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.39 - 8.81 (1H, br s, H7), 7.80 (2H, d, *J* = 9.0 Hz, H4), 6.97 (2H, d, *J* = 9.0 Hz, H3), 4.20 (2H, q, *J* = 6.8 Hz, H8), 3.79 (3H, s, H1), 1.31 (2H, t, *J* = 6.8 Hz, H9)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 161.2 (C6), 131.3 (C2), 128.6 (C4), 114.1 (C5), 113.7 (C3), 60.6 (C8), 55.4 (C1), 14.3 (C9)

HRMS (ESI+): found $[M + H]^+$180.1020, $C_{10}H_{14}NO_2^+$ required 180.1025

This data is in accordance with that previously reported.[290]

5.2.1.7. Ethyl 2-(4-bromophenyl)acetimidate (82)



Following General Procedure 1: 4-bromophenylacetonitrile **75** (1.70 g, 8.67 mmol), acetyl chloride (4.55 mL, 64.0 mmol) and ethanol (5.6 mL, 96.0 mmol) were used the yield the title compound **82** as a yellow liquid (1.94 g, 8.01 mmol, 92%).

R_f = 0.77 (EtOAc)

IR ν_{max} = 3413 (s, N-H), 3109 (m, C-H), 1626 (s, C=N), 1626 (s, C=C), 1523 (m, C=C)

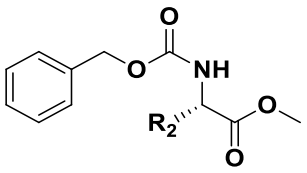
^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.50 (2H, d, *J* = 8.5 Hz, H2), 7.23 (2H, d, *J*=8.5 Hz, H3), 4.07 (2H, q, *J* = 7.2 Hz, H8), 3.66 (2H, s, H5), 1.17 (3H, t, *J* = 7.2 Hz, H9)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 170.8 (C6), 134.0 (C4), 131.4 (C2), 131.2 (C3), 120.1 (C1), 60.4 (C8), 39.0 (C5), 14.1 (C9)

HRMS (ESI+): found $[M + H]^+$ 242.0185, $C_{10}H_{13}BrNO^+$ required 242.0180

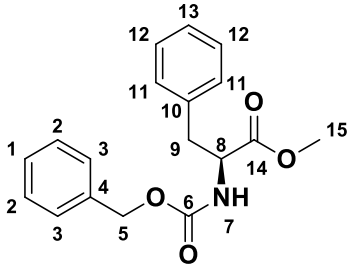
This data is in accordance with that previously reported.[291]

5.2.2. General procedure for the formation of Methyl ((benzyloxy)carbonyl) amino esters



General Procedure 2: Thionyl chloride (1.4 eq.) was added dropwise over 10 minutes to a stirred solution of the *N*-(benzyloxycarbonyl)amino acid in methanol (0.2 M) at 0 °C. The mixture was stirred for 2 hours until the acid had been consumed. The methanol was removed under reduced pressure. The crude compound was purified by flash column chromatography on silica to yield the title compound.

5.2.2.1. Methyl ((benzyloxy)carbonyl)-L-phenylalaninate (51)



Following General Procedure 2: (benzyloxycarbonyl)-*L*-phenylalanine **49** (12.0 g, 40.1 mmol), thionyl chloride (4.09 mL, 56.1 mmol) and methanol (200 mL) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (100%) to yield the title compound **51** as a cloudy oil (12.53 g, 39.9 mmol, 99%).

R_f = 0.70 (EtOAc)

$[\alpha]_D^{20}$ = -13.2 (c = 1.0 in CH_3OH) - [Literature Value = -14.4 (c = 1.3 in CH_3OH)][292]

IR ν_{max} = 3344 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1704 (s, br, C=O), 1497 (m, C=C), 1454 (m, C=C), 1406 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.38-7.31 (5H, m, H1, 2 & 3), 7.30-7.23 (3H, m, H12 & 13), 7.12 (2H, dd, J = 7.9, 1.5 Hz, H11), 5.23 (1H, d, J = 5.8 Hz, H7), 5.12 (1H, d, J = 12.2 Hz, H5a) 5.09 (1H,

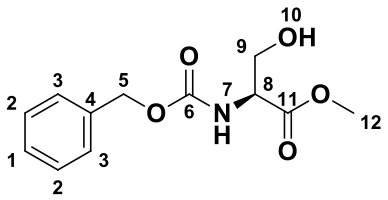
d, J = 12.2 Hz, H5b), 4.68 (1H, dt, J = 6.1, 5.8 Hz, H8), 3.74 (3H, s, H15), 3. 16 (1H, dd, J = 13.7, 5.8 Hz, H9a), 3.11 (1H, dd, J = 13.8, 6.1 Hz, H9b)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 171.9 (C14), 155.6 (C6), 136.2 (C4), 135.6 (C10), 129.2 (C11), 128.6 (C1), 128.5 (C2), 128.2 (C12), 128.1 (C3), 127.1 (C13), 67.0 (C5), 54.8 (C8), 52.3 (C15), 38.2 (C9)

HRMS (ESI+): found $[M + H]^+$ 314.1382, $C_{18}H_{20}NO_4^+$ required 314.1392

This data is in accordance with that previously reported.[292]

5.2.2.2. Methyl ((benzyloxy)carbonyl)-L-serinate (89)



Following General Procedure 2: methyl-(benzyloxycarbonyl)-*L*-serine **83** (9.9 g, 41.4 mmol), thionyl chloride (4.23 mL, 57.9 mmol) and methanol (165 mL) were used. The crude product was purified by flash column chromatography eluting with 40% ethyl acetate in 40-60 petroleum ether to yield the title compound **89** as a pale-yellow oil (10.5 g, 41.3 mmol, 100%).

R_f = 0.29 (40% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -12.6 (c = 1.2 in CH_3OH) - [Literature Value = -13.2 (c = 10.0 in CH_3OH)][293]

IR ν_{max} = 3359 (w, N-H), 3250 (w, br, O-H), 2987 (s, C-H), 2901 (s, C-H), 1695 (s, br, C=O), 1515 (m, C=C), 1453 (m, C=C), 1438 (m, C=C), 1406 (m, C=C)

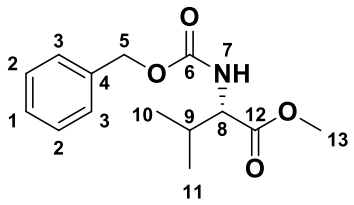
^{1}H NMR (400 MHz, d_6-DMSO): δ_H = 7.54 (1H, d, *J* = 8.2 Hz, H7), 7.35 - 7.40 (4H, m, H2 & 3), 7.29 - 7.34 (1 H, m, H1) 5.04 (2H, s, H5), 4.97 (1 H, t, *J* = 6.0 Hz, H10) 4.15 (1H, dt, *J* = 8.2, 5.2 Hz, H8), 3.66 (2H, t, *J*=5.2 Hz, H9), 3.63 (3H, s, H12),

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 171.4 (C11), 156.1 (C6), 137.0 (C4), 128.5 (C2), 128.0 (C1), 127.9 (C3), 65.7 (C5), 61.3 (C9), 56.8 (C8), 52.0 (C12)

HRMS (ESI+): found $[M + H]^+$ 254.1032, $C_{12}H_{16}NO_5^+$ required 254.1028

This data is in accordance with that previously reported.[293]

5.2.2.3. Methyl ((benzyloxy)carbonyl)-L-valinate (90)



Following General Procedure 2: methyl-(benzyloxycarbonyl)-*L*-valine **84** (9.90 g, 39.4 mmol), thionyl chloride (4.03 mL, 55.2 mmol) and methanol (165 mL) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (100%) to yield the title compound **90** as a cloudy oil (10.5 g, 39.4 mmol, 100%).

R_f = 0.68 (EtOAc)

$[\alpha]_D^{20}$ = -19.7 (c = 1.0 in CH_3OH) - [Literature Value = -19.4 (c = 1.0 in CH_3OH)][294]

IR ν_{max} = 3364 (w, N-H), 2972 (s, C-H), 2901 (s, C-H), 1705 (s, br, C=O), 1512 (m, C=C), 1454 (m, C=C), 1436 (m, C=C), 1406 (m, C=C)

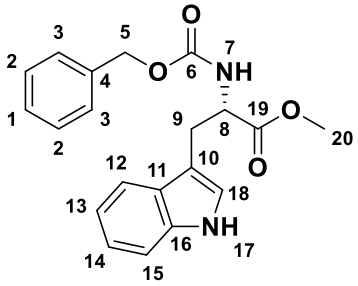
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 7.63 - 7.74 (1H, d, *J* = 8.1 Hz, H7), 7.33 - 7.40 (4H, m, H2 & H3), 7.29 - 7.33 (1H, m, H1), 5.03 (2H, s, H5), 3.92 (1H, dd, *J* = 8.1, 6.5 Hz, H8), 3.63 (3H, s, H13), 2.02 (1H, qd, *J* = 6.8, 6.5 Hz, H9), 0.87 (3H, d, *J* = 6.8 Hz, H10/11), 0.86 (3H, d, *J* = 6.8 Hz, H10/11)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 127.8 (C12), 156.8 (C6), 137.4 (C4), 128.8 (C2), 128.3 (C1), 128.2 (C3), 66.0 (C5), 60.2 (C8), 52.1 (C13), 30.1 (C9), 19.4, 18.7 (C10 & 11)

HRMS (ESI+): found $[M + Na]^+$ 266.1386, $C_{14}H_{20}NO_4^+$ required 266.1387

This data is in accordance with that previously reported.[294]

5.2.2.4. Methyl ((benzyloxy)carbonyl)-L-tryptophanate (91)



Following General Procedure 2: methyl-(benzyloxycarbonyl)-*L*-tryptophan **85** (2.00 g, 5.91 mmol), thionyl chloride (0.60 mL, 8.27 mmol) and methanol (30 mL) were used. The crude product was purified by flash column chromatography eluting with 40% ethyl acetate in 40-60 petroleum ether to yield the title compound **91** as a brown oil (2.05 g, 5.82 mmol, 98%).

$\mathbf{R_f}$ = 0.63 (40% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -10.1 (c = 0.7 in CH_3OH) - [Literature Value = -11.0 (c = 0.4 in CH_3OH)][295]

IR ν_{max} = 3407 (w, br, N-H), 2988 (s, C-H), 2901 (s, C-H), 1697 (s, br, C=O), 1507 (m, C=C), 1455 (m, C=C), 1435 (m, C=C), 1407 (m, C=C)

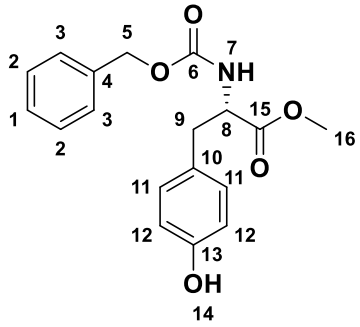
^{1}H NMR (400 MHz, d_6-DMSO): δ_H = ppm 10.88 (1H, br s, H17), 7.79 (1H, d, *J* = 7.8 Hz, H7), 7.51 (1H, d, *J* = 7.5 Hz, H12), 7.25 - 7.38 (4H, m, H1, 2, 3 & 15), 7.17 (1H, d, *J* = 1.4 Hz, H18), 7.07 (1H, t, *J* = 7.2 Hz, H14), 6.95 - 7.02 (1H, m, H13), 4.92 - 5.06 (2H, m, H5), 4.21 - 4.41 (1H, m, H8), 3.61 (3H, s, H20), 3.19 (1H, dd, *J* = 14.8, 5.2 Hz, H9a), 3.03 (1H, dd, *J* = 14.8, 9.2 Hz, H9b)

^{13}C NMR (101 MHz, d_6-DMSO): δ_C = 172.8 (C19), 156.1 (C6), 136.9 (C4), 136.2 (C16), 128.4 (C2), 127.9 (C1), 127.7 (C3), 127.1 (C11) 123.9 (C18), 121.1 (C14), 118.5 (C13), 118.1 (C12), 111.6 (C15), 109.7 (C10), 65.2 (C5), 55.1 (C8), 52.0 (C20), 27.0 (C9)

HRMS (ESI+): found $[M + H]^+$ 353.1500, $C_{20}H_{21}N_2O_4^+$ required 353.1501

This data is in accordance with that previously reported.[295]

5.2.2.5. Methyl ((benzyloxy)carbonyl)-L-tyrosinate (92)



Following General Procedure 2: methyl-(benzyloxycarbonyl)-*L*-tyrosine **86** (2.00 g, 6.34 mmol), thionyl chloride (0.65 mL, 8.88 mmol) and methanol (35 mL) were used. The crude product was purified by flash column chromatography eluting with 40% ethyl acetate in 40-60 petroleum ether to yield the title compound **92** as a yellow-orange oil (2.09 g, 6.34 mmol, 100%).

R_f = 0.54 (40% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -7.2 (c = 0.9 in CH_3OH) - [Literature Value = -7.9 (c = 0.5 in CH_3OH)][296]

IR ν_{max} = 3362 (w, br, O-H), 3360 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1694 (s, br, C=O), 1513 (s, C=C), 1437 (s, C=C), 1407 (s, C=C)

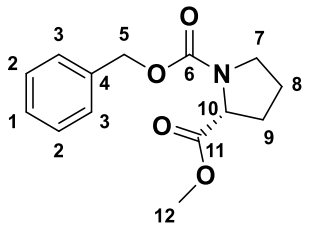
^{1}H NMR (400 MHz, d_6-DMSO): δ_H = 9.27 (1H, s, H14), 7.77 (1H, d, *J* = 8.2 Hz, H7), 7.19 - 7.49 (5H, m, H1, 2 & 3), 7.02 (2H, d, *J* = 7.5 Hz, H11), 6.68 (2H, d, *J* = 7.5 Hz, H12), 4.98 (2H, s, H5), 4.04 - 4.31 (1H, m, H8), 3.61 (3H, s, H16), 2.91 (1H, dd, *J* = 13.6, 4.4 Hz, H9a), 2.67 - 2.81 (1H, m, H9b)

^{13}C NMR (101 MHz, d_6-DMSO): δ_C = 172.6 (C15), 156.1 (C13), 137.0 (C6), 130.1 (C11), 128.4 (C2), 127.8 (C1), 127.6 (C3), 127.4 (C10), 115.1 (C12), 65.4 (C5), 56.0 (C8), 52.0 (C16), 35.9 (C9)

HRMS (ESI+): found $[M + H]^+$ 352.1152, $C_{18}H_{19}NO_5S^+$ required 352.1155

This data is in accordance with that previously reported.[296]

5.2.2.6. Methyl ((benzyloxy)carbonyl)-L-prolinate (93)



Following General Procedure 2: methyl-(benzyloxycarbonyl)-*L*-proline **87** (2.00 g, 8.02 mmol), thionyl chloride (0.82 mL, 11.2 mmol) and methanol (40 mL) were used. The crude product was purified by flash column chromatography eluting with 40% ethyl acetate in 40-60 petroleum ether to yield the title compound **93** as a yellow oil (2.02 g, 7.67 mmol, 96%).

$\mathbf{R_f}$ = 0.45 (40%EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -52.8 (c = 1.0 in CH_3OH) - [Literature Value = -57.0 (c = 1.0 in CH_3OH)][297]

IR ν_{max} = 2988 (s, C-H), 2901 (s, C-H), 1744 (s, C=O), 1699 (s, C=O), 1409 (s, C=C)

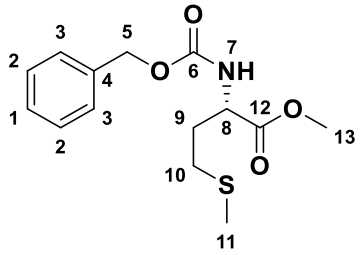
^{1}H NMR (400 MHz, d_6-DMSO): δ_H = 7.22 - 7.42 (5H, m, H1, 2 & 3), 4.92 - 5.14 (2H, m, H5), 4.22 - 4.36 (1H, m, H10), 3.52 - 3.68 (3H, m, H12), 3.30 - 3.50 (2H, m, H7), 2.12 - 2.33 (1H, m, H9a), 1.74 - 1.96 (3H, m, H8 & 9b) – Mixture of rotamers

^{13}C NMR (101 MHz, d_6-DMSO): δ_C = 173.1, 172.8 (C11), 154.1, 153.5 (C6), 137.0, 136.9 (C4), 128.5, 128.4 (C2), 127.9, 127.8 (C1), 127.6, 127.3 (C3), 66.1, 66.1 (C5), 58.9, 58.4 (C10), 52.0 (C12), 46.9, 46.3 (C7), 30.5, 29.5 (C9), 24.1, 23.2 (C8)

HRMS (ESI+): found $[M + Na]^+$ 286.1046, $C_{14}H_{17}NO_4Na^+$ required 286.1055

This data is in accordance with that previously reported.[297]

5.2.2.7. Methyl ((benzyloxy)carbonyl)-L-methioninate (94)



Following General Procedure 2: methyl-(benzyloxycarbonyl)-*L*-methionine **88** (2.00 g, 7.06 mmol), thionyl chloride (0.72 mL, 9.88 mmol) and methanol (35 mL) were used. The crude product was purified by flash column chromatography eluting with 40% ethyl acetate in 40-60 petroleum ether to yield the title compound **94** as a yellow oil (2.10 g, 7.06 mmol, 100%).

R_f = 0.88 (40% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -32.5 (c = 1.1 in CH_3OH) - [Literature Value = -34.1 (c = 1.1 in CH_3OH)][298]

IR ν_{max} = 3339 (m, N-H), 2988 (s, C-H), 2901 (s, C-H), 1746 (s, C=O), 1685 (s, C=O), 1526 (s, C=C), 1443 (m, C=C), 1406 (m, C=C)

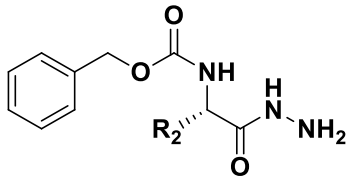
^{1}H NMR (400 MHz, d_6-DMSO): δ_H = 7.79 (1H, d, *J* = 7.8 Hz, H7), 7.24 - 7.44 (5H, m, H1, 2 & 3), 5.04 (2H, s, H5), 4.15 - 4.27 (1H, m, H8), 3.64 (3H, s, H13), 2.52 - 2.48 (2H, m, H10), 2.02 (3H, s, H11), 1.80 - 1.98 (2H, m, H9)

^{13}C NMR (101 MHz, d_6-DMSO): δ_C = 172.7 (C12), 156.2 (C6), 137.0 (C4), 128.5 (C2), 128.0 (C1), 127.8 (C3), 65.6 (C5), 52.8 (C8), 52.1 (C13), 30.3 (C9), 29.6 (C10), 14.6 (C11)

HRMS (ESI+): found $[M + Na]^+$ 320.0920, $C_{14}H_{19}NO_4SNa^+$ required 320.0927

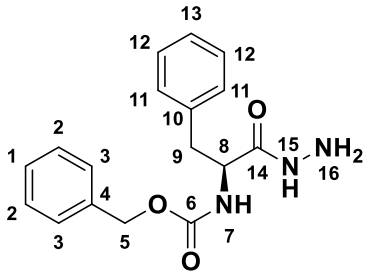
This data is in accordance with that previously reported.[298]

5.2.3. General procedure for the formation of Methyl ((benzyloxy)carbonyl) amino hydrazides



General Procedure 3: A solution of the methyl ((benzyloxy)carbonyl) amino ester and hydrazine monohydrate (5 eq.) in methanol (0.5 M) was stirred overnight at room temperature. Water (0.25 M) was added and the product collected by vacuum filtration. The title compound was carried forward without further purification.

5.2.3.1. Benzyl (S)-(1-hydrazinyl-1-oxo-3-phenylpropan-2-yl)carbamate (52)



Following General Procedure 3: methyl ((benzyloxy)carbonyl)-*L*-phenylalaninate **51** (12.92 g, 41.2 mmol) and hydrazine monohydrate (10 mL, 206 mmol) in methanol (85 mL) were used to yield the title compound **52** as a white solid (12.24 g, 39.1 mmol, 95%).

$\mathbf{R_f}$ = 0.23 (EtOAc)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -4.2 (c = 1.1 in CH_3OH) - [Literature Value = +10.3 (c = 1.0 in CH_3OH)][299]

IR ν_{max} = 3298 (m, N-H), 2988 (s, C-H), 2901 (s, C-H), 1688 (m, C=O), 1651 (m, C=O), 1626 (m, C=C), 1606 (m, C=C), 1535 (s, C=C), 1493 (w, C=C), 1454 (w, C=C)

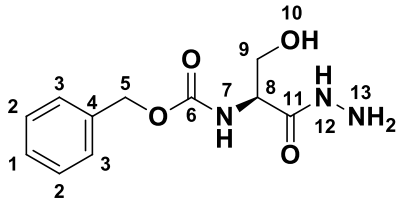
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 9.22 (1H, br s, H15), 7.52 (1H, d, *J* = 8.5 Hz, H7), 7.03 - 7.41 (10H, m, H1, 2, 3, 11, 12 & 13), 4.91 (2H, s, H5), 4.23 - 4.40 (2H, br, H16), 4.18 (1H, ddd, *J* = 10.2, 8.5, 4.4 Hz, H8), 2.90 (1H, dd, *J* = 13.7, 4.4 Hz, H9a), 2.76 (1H, dd, *J* = 13.7, 10.2 Hz, H9b)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 170.8 (C14), 155.8 (C6), 138.2 (C10), 137.1 (C4), 129.3 (C12), 128.4, 128.1 (C2 & 11), 127.8 (C1), 127.6 (C3), 126.3 (C13), 65.2 (C5), 55.0 (C8), 37.8 (C9)

HRMS (ESI+): found $[M + H]^+$ 314.1505, $C_{17}H_{20}N_3O_3^+$ required 314.1505

This data is in accordance with that previously reported.[299]

5.2.3.2. Benzyl (S)-(1-hydrazinyl-3-hydroxy-1-oxopropan-2-yl)carbamate (95)



Following General Procedure 3: methyl ((benzyloxy)carbonyl)-*L*-serinate **89** (9.00 g, 35.5 mmol) and hydrazine monohydrate (8.62 mL, 178 mmol) in methanol (65 mL) were used to yield the title compound **95** as a white solid (7.74 g, 30.5 mmol, 86%).

R_f = 0.48 (EtOAc)

$[\alpha]_D^{20}$ = -18.0 (c = 1.0 in CH_3OH)

IR ν_{max} = 3282 (s, br, O-H, N-H), 2988 (s, C-H), 2901 (s, C-H), 1690 (s, C=O), 1651 (s, C=O), 1615 (m, C=C), 1536 (s, C=C), 1463 (m, C=C), 1451 (m, C=C)

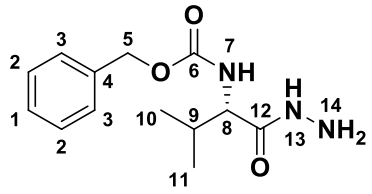
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 9.10 (1H, br s, H12), 7.35 - 7.40 (4H, m, H2 & 3), 7.27 - 7.34 (1H, m, H1) 7.15 (1H, d, *J* = 8.5 Hz, H7), 5.02 (2H, s, H5), 4.84 (1H, t, *J* = 5.8 Hz, H10), 4.21 (2H, br s, H13), 4.02 (1H, dt, *J* = 8.5, 6.0 Hz, H8), 3.47 - 3.58 (2H, m, H9)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 169.8 (C11), 156.2 (C6), 137.5 (C4), 128.8 (C2), 128.2 (C1), 128.2 (C3), 65.9 (C5), 62.2 (C9), 56.5 (C8)

HRMS (ESI+): found $[M + H]^+$ 254.1135, $C_{11}H_{16}N_3O_4^+$ required 254.1141

This data is in accordance with that previously reported.[300]

5.2.3.3. Benzyl (S)-(1-hydrazinyl-3-methyl-1-oxobutan-2-yl)carbamate (96)



Following General Procedure 3: methyl ((benzyloxy)carbonyl)-*L*-valinate **90** (9.00 g, 33.92 mmol) and hydrazine monohydrate (8.23 mL, 169 mmol) in methanol (65 mL) were used to yield the title compound **96** as a white solid (8.85 g, 33.4 mmol, 98%).

R_f = 0.78 (EtOAc)

$[\alpha]_D^{20}$ = +6.6 (c = 1.0 in DMF) - [Literature Value = -12.6 (c = 1.0 in CH_3OH)][299]

IR ν_{max} = 3313 (m, N-H), 3246 (m, N-H), 2971 (s, C-H), 2901 (s, C-H), 1683 (m, C=O), 1656 (s, C=O), 1527 (s, C=C), 1469 (m, C=C), 1454 (m, C=C)

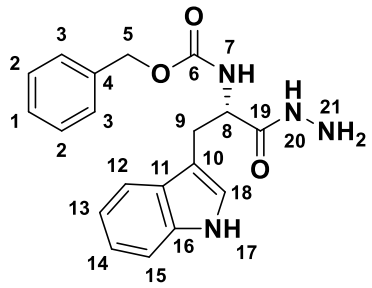
^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 9.09 (1H, br s, H13), 7.28 - 7.37 (5H, m, H1, 2 & 3), 7.25 (1H, d, *J* = 8.4 Hz, H7), 4.98 (2H, s, H5), 4.21 (2H, d, *J* = 4.0 Hz, H14), 3.73 (1H, t, *J* = 8.4 Hz, H8), 1.88 (1H, dq, *J* = 8.4, 6.7 Hz, H9), 0.83 (3H, d, *J* = 6.7 Hz, H10/11), 0.81 (3H, d, *J* = 6.7 Hz, H10/11)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 170.9 (C12), 156.4 (C6), 137.6 (C4), 128.8 (C2), 128.2 (C1), 128.1 (C3), 65.8 (C5), 59.5 (C8), 30.7 (C9), 19.6, 19.0 (C10 & 11)

HRMS (ESI+): found $[M + H]^+$ 266.1494, $C_{13}H_{20}N_3O_3^+$ required 266.1505

This data is in accordance with that previously reported.[299]

5.2.3.4. Benzyl (S)-(1-hydrazinyl-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate (97)



Following General Procedure 3: methyl ((benzyloxy)carbonyl)-*L*-tryptophanate **91** (2.00 g, 4.26 mmol) and hydrazine monohydrate (1.38 mL, 28.4 mmol) in methanol (10 mL) were used to yield the title compound **97** as a beige solid (1.24 g, 3.51 mmol, 82%).

$\mathbf{R_f}$ = 0.80 (EtOAc)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -20.6 (c = 1.0 in DMF)

IR ν_{max} = 3431 (w, N-H), 3296 (m, N-H), 3248 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1682 (s, C=O), 1648 (s, C=O). 1619 (m, C=C), 1538 (m, C=C), 1461 (m, C=C), 1490 (m, C=C)

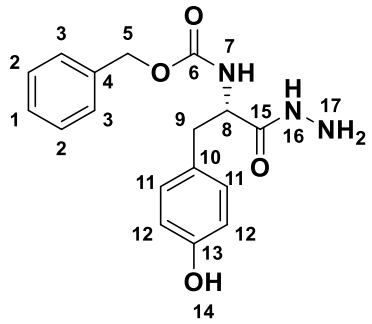
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 10.79 (1H, br s, H17), 9.24 (1H, s, H20), 7.61 (1H, d, *J* = 7.5 Hz, H12), 7.40 (1H, d, *J* = 8.2 Hz, H7), 7.20 - 7.35 (6H, m, H1, 2, 3 & 15), 7.13 (1H, s, H18), 7.05 (1H, t, *J* = 7.5 Hz, H14), 6.96 (1H, t, *J* = 7.5 Hz, H13), 4.94 (1H, d, *J* = 12.5 Hz, H5a), 4.90 (1H, d, *J* = 12.5 Hz, H5b), 4.11 - 4.39 (2H, m, H8), 3.03 (1H, dd, *J* = 14.5, 5.0 Hz, H9a), 2.90 (1H, dd, *J* = 14.5, 9.6 Hz, H9b)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 171.2 (C19), 155.8 (C6), 137.1 (C4), 136.1 (C16), 128.4 (C2), 127.8 (C1), 127.6 (C3), 127.3 (C11), 123.9 (C18), 120.9 (C14), 118.6, 118.3 (C12 & 13), 111.4 (C15), 110.2 (C10), 65.3 (C5), 54.2 (C8), 28.1 (C9)

HRMS (ESI+): found $[M + H]^+$ 353.1622, $C_{19}H_{21}N_4O_3^+$ required 353.1614

This data is in accordance with that previously reported.[301]

5.1.3.5. Benzyl (S)-(1-hydrazinyl-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamate (98)



Following General Procedure 3: methyl ((benzyloxy)carbonyl)-*L*-tyrosinate **92** (1.50 g, 4.55 mmol) and hydrazine monohydrate (1.10 mL, 22.8 mmol) in methanol (10 mL) were used to yield the title compound **98** as a white solid (1.27 g, 3.86 mmol, 85%).

R_f = 0.78 (EtOAc)

$[\alpha]_D^{20}$ = -11.9 (c = 0.6 in DMF) - [Literature Value = -11.2 (c = 1.0 in DMF)][302]

IR ν_{max} = 3295 (m, N-H), 3267 (m, O-H), 2988 (s, C-H), 2901 (s, C-H), 1689 (s, C=O), 1665 (s, C=O), 1625 (m, C=C), 1532 (m, C=C), 1513 (m, C=C0, 1453 (m, C=C)

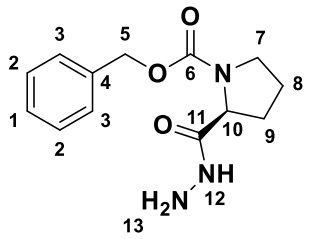
^{1}H NMR (400 MHz, d_6-DMSO): δ_H = 9.17 (1H, s, H16/17), 9.16 (1H, s, H16/17), 7.44 (1H, d, *J* = 8.9 Hz, H7), 7.20 - 7.36 (5H, m, H1, 2 & 3), 7.03 (2H, d, *J* = 8.7 Hz, H11), 6.63 (1H, d, *J* = 8.7 Hz, H12), 4.92 (2H, s, H5), 4.21 (2H, br S, H17), 4.09 (1H, ddd, *J* = 10.2, 8.9, 4.8 Hz, H8), 2.77 (1H, dd, *J* = 13.6, 4.8 Hz, H9a), 2.62 (1H, dd, *J* = 13.6, 10.2 Hz, H9b)

^{13}C NMR (101 MHz, d_6-DMSO): δ_C = 171.0 (C15), 155.8, 155.7 (C6 & 13) 137.2 (C4), 130.2 (C11), 128.4 (C2), 128.2 (C10), 127.7 (C1), 127.5 (C3), 114.9 (C12), 65.2 (C5), 55.4 (C8), 37.1 (C9)

HRMS (ESI+): found $[M + H]^+$ 330.1467, $C_{17}H_{20}N_3O_4^+$ required 330.1454

This data is in accordance with that previously reported.[302]

5.2.3.6. Benzyl (S)-2-(hydrazinecarbonyl)pyrrolidine-1-carboxylate (99)



Following General Procedure 3: methyl ((benzyloxy)carbonyl)-*L*-pyrrolinate **93** (1.50 g, 5.70 mmol) and hydrazine monohydrate (1.38 mL, 28.5 mmol) in methanol (12 mL) were used to yield the title compound **99** as a brown solid (1.44 g, 5.47 mmol, 96%).

R_f = 0.68 (EtOAc)

$[\alpha]_D^{20}$ = -48.5 (c = 1.0 in CH_3OH)

IR ν_{max} = 3315 (w, br, N-H), 3248 (w, br, N-H), 2987 (s, C-H), 2901 (s, C-H), 1659 (s, br, C=O), 1520 (m, C=C), 1411 (s, C=C)

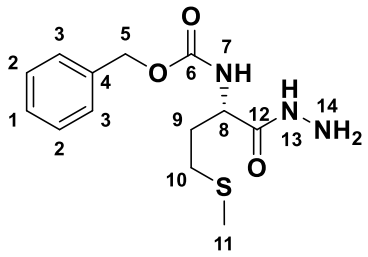
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 9.15 (2H, d, *J* = 11.9 Hz, H12), 7.25 - 7.44 (10H, m, H1, 2 & 3), 5.00 - 5.10 (4H, m, H5), 4.21 (2H, br s, H13), 4.16 (1H, dd, *J* = 8.2, 3.4 Hz, H10), 4.12 (1H, dd, *J* = 8.4, 3.2 Hz, H10), 3.37 - 3.52 (4H, m, H7), 2.01 - 2.17 (2H, m, H9a), 1.73 - 1.91 (6H, m, H8 & 9b) – mixture of rotamers

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 171.9, 171.6 (C11), 154.4, 154.2 (C6), 137.5 (C4), 128.8, 128.8 (C2), 128.2, 128.0 (C1), 127.9, 127.5 (C3), 66.3, 66.2 (C5), 59.3, 58.7 (C10), 47.5, 46.9 (C7), 31.6, 30.5 (C9), 24.4, 23.5 (C8)

HRMS (ESI+): found $[M + H]^+$ 264.1336, $C_{13}H_{18}N_3O_3^+$ required 264.1348

This data is in accordance with that previously reported.[303]

5.2.3.7. Benzyl (S)-(1-hydrazinyl-4-(methylthio)-1-oxobutan-2-yl)carbamate (100)



Following General Procedure 3: methyl ((benzyloxy)carbonyl)-*L*-methionate **88** (1.05 g, 3.53 mmol) and hydrazine monohydrate (0.86 mL, 17.6 mmol) in methanol (10 mL) were used to yield the title compound **100** as a grey solid (849 mg, 2.86 mmol, 81%).

R_f = 0.80 (EtOAc)

$[\alpha]_D^{20}$ = -17.9 (c = 1.0 in CH_3OH) - [Literature Value = -14.1 (c = 1.0 in CH_3OH)][304]

IR ν_{max} = 3289 (s, N-H), 2988 (s, C-H), 2901 (s, C-H), 1691 (s, C=O), 1649 (s, C=O), 1534 (s, C=C), 1443 (m, C=C)

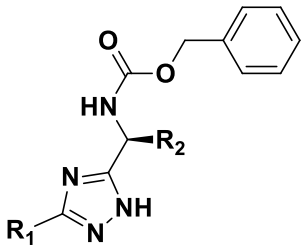
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 9.11 (1H, br s, H13), 7.44 (1H, d, *J* = 8.2 Hz, H7), 7.32 - 7.38 (3H, m, H1 & 3), 7.26 - 7.32 (2H, m, H2), 4.99 (2H, s, H5), 4.20 (2H, br s, H14), 4.02 (1H, td, *J* = 8.2, 5.8 Hz, H8), 2.35 - 2.48 (2H, m, H10), 2.01 (3H, s, H11), 1.73 - 1.88 (2H, m, H9)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 170.8 (C13), 155.9 (C6), 137.1 (C4), 128.4 (C2), 127.9 (C1), 127.8 (C3), 65.5 (C5), 52.6 (C8), 31.8 (C9), 29.7 (C10), 14.6 (C11)

HRMS (ESI+): found $[M + H]^+$ 298.1219, $C_{17}H_{20}N_3O_3S^+$ required 298.1225

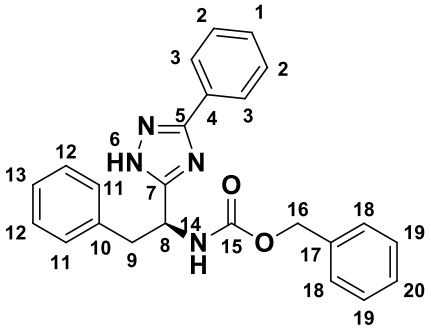
This data is in accordance with that previously reported.[304]

5.2.4. General procedure for the formation of Benzyl –(S)-(2-R_2-((3-R_1-1H-1,2,4-triazol-5-yl)methyl)carbamates



General Procedure 4: A stirred solution of the required imidate (1.2 eq.) and methyl ((benzyloxy)carbonyl) amino hydrazide (1.0 eq.) in ethanol (0.5 M) was heated at reflux for 2 hours. Acetic acid (1 M) was added and the solution was refluxed for 2 hours. The solvent was removed under reduced pressure. The resultant crude product was purified by flash column chromatography to yield the title compound

5.2.4.1. Benzyl (S)-(2-phenyl-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate (54)



Following General Procedure 4: ethyl benzimidate **53** (4.00 g, 12.8 mmol) and benzyl (*S*)-(1-hydrazinyl-1-oxo-3-phenylpropan-2-yl)carbamate **52** (2.28 g, 15.3 mmol) in ethanol (25 mL), followed by acetic acid (13 mL) were used. The crude product was purified by flash column chromatography eluting with 50% ethyl acetate in hexane to yield the title compound **54** as a white solid (4.35 g, 10.9 mmol, 85%).

$\mathbf{R_f}$ = 0.56 (50% EtOAc in hexane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -6.1 (c = 0.4 in CH_3OH)

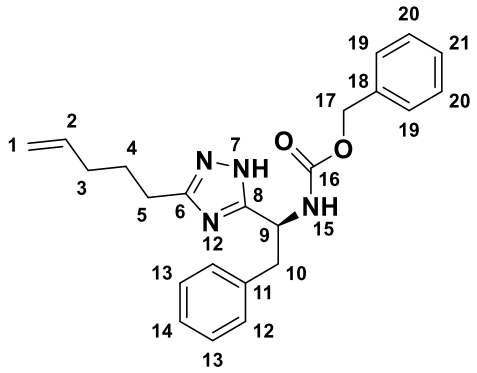
IR ν_{max} = 3250 (w, br, N-H), 2988 (s, C-H), 2901 (s, C-H), 1691 (s, C=O), 1495 (m, C=C), 1454 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.01 (2H, d, *J* = 7.0 Hz, H3), 7.50 (3H, br s, H 1 & 2), 7.33 (2H, d, *J* = 7.3 Hz, H18/19), 7.30 (1H, d, *J* = 7.3 Hz, H20), 7.25 - 7.29 (6H, m, H11, 12 & 18/19), 7.22 (1H, dt, *J* = 8.2, 4.1 Hz, H13), 5.00 (1H, d, *J* = 12.8 Hz, H16a), 4.96 (2H, d, *J* = 12.8 Hz, H8 & 16b), 3.29 (1H, dd, *J* = 13.6, 4.4 Hz, H9a), 3.10 (1H, t, *J* = 13.6 Hz, H9b)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 161.0 (C7), 158.1 (C5), 155.8 (C15), 138.0 (C17), 137.2 (C10), 131.5 (C4), 129.3 (C12), 128.9 (C1), 128.3 (C2), 128.2, 128.1 (C11 & 19) 127.7 (C20), 127.5 (C18), 126.4 (C13), 125.9 (C3), 65.3 (C16), 49.8 (C8), 39.5 (C9)

HRMS (ESI+): found $[M + H]^+$ 399.1814, $C_{24}H_{23}N_4O_2^+$ required 399.1816.

5.2.4.2. Benzyl (S)-(1-(3-(pent-4-en-1-yl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (101)



Following General Procedure 4: ethyl hex-5-enimidate **77** (0.65 g, 4.62 mmol) and benzyl (*S*)-(1-hydrazinyl-1-oxo-3-phenylpropan-2-yl)carbamate **52** (1.21 g, 3.85 mmol) in ethanol (8 mL), followed by acetic acid (4 mL) were used. The crude product was purified by flash column chromatography eluting with 40% ethyl acetate in 40-60 petroleum ether to yield the title compound **101** as a yellow liquid (1.29 g, 3.30 mmol, 86%).

R_f = 0.32 (40% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -15.9 (c = 0.4 in CH_3OH)

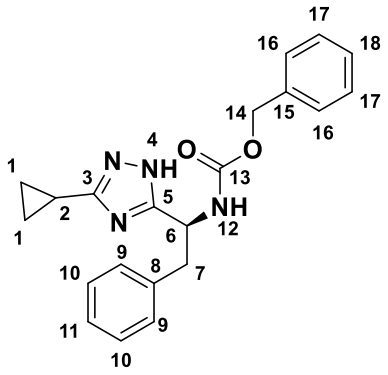
IR ν_{max} = 3237 (w, N-H), 2988 (s, C-H), 2902 (s, C-H), 1694 (s, C=O), 1522 (m, C=C), 1495 (m, C=C), 1454 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 13.34 - 13.43 (1H, m, H7), 7.68 (1H, d, *J* = 9.2 Hz, H15), 7.27 - 7.36 (3H, m, H12/19 & 21), 7.15 - 7.26 (7H, m, H12/19, 13, 14 & 20), 5.83 (1H, ddd, *J* = 17.1, 10.4, 7.5 Hz, H2), 4.91 - 5.08 (4H, m, H1 & 17), 4.83 (1H, td, *J* = 9.6, 5.5 Hz, H9), 3.15 (1H, dd, *J* = 13.7, 5.5 Hz, H10a), 2.98 (1H, dd, *J* = 13.7, 9.6 Hz, H10b), 2.68 (2H, t, *J* = 7.5 Hz, H5), 2.06 (2H, q, *J* = 7.5 Hz, H3), 1.75 (2H, quin, *J* = 7.5 Hz, H4)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 164.0 (C8), 157.0 (C6), 156.1 (C16), 139.0 (C11), 138.4 (C2), 137.7 (C18), 129.7 (C13), 128.7, 128.4 (C12 & 19), 128.0 (C21), 127.8 (C19), 126.5 (C14), 115.8 (C1), 65.4 (C17), 51.5 (C9), 39.5 (C10), 33.0 (C3), 27.0 (C4), 25.6 (C5)

HRMS (ESI+): found $[M + H]^+$ 391.2122, $C_{23}H_{26}N_4O_2^+$ required 391.2134.

5.2.4.3. Benzyl (S)-(1-(3-cyclopropyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (102)



Following General Procedure 4: ethyl cyclopropanecarbimidate **78** (0.95 g, 8.42 mmol) and benzyl (*S*)-(1-hydrazinyl-1-oxo-3-phenylpropan-2-yl)carbamate **52** (2.10 g, 7.02 mmol) in ethanol (14 mL), followed by acetic acid (7 mL) were used. The crude product was purified by flash column chromatography eluting with 50% ethyl acetate in 40-60 petroleum ether to yield the title compound **102** as a white solid (2.07 g, 5.71 mmol, 81%).

R_f = 0.30 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -16.0 (c = 0.2 in CH_3Cl)

IR ν_{max} = 3315 (m, N-H), 2988 (s, C-H), 2901 (s, C-H), 1682 (s, C=O), 1511 (m, C=C), 1452 (w, C=C), 1393 (m, C=C)

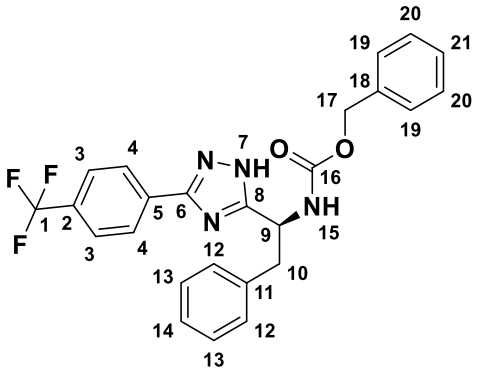
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 17.87 (1H, d, *J* = 7.9 Hz, H4), 7.64 (1H, d, *J* = 8.9 Hz, H12), 7.26 - 7.36 (3H, m, H17 & 18), 7.13 - 7.25 (7H, m, H9, 10, 11 & 16), 4.88 - 5.00 (2H, m, H14), 4.77

(1H, dd, *J* = 10.4, 5.8 Hz, H6), 3.11 (1H, dd, *J* = 13.5, 5.8 Hz, H7a), 2.95 (1H, dd, *J* = 13.5, 10.4 Hz, H7b), 1.88 - 2.02 (1H, m, H2), 0.99 (2H, d, *J* = 6.1 Hz, H1a), 0.86 (2H, br s, H1b)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 163.4 (C5), 158.6 (C3), 155.6 (C13), 138.5 (C8), 137.3 (C15), 129.2 (C10), 128.2, 128.0 (C9 & 17), 127.6 (C18), 127.3 (C16), 126.1 (C11), 64.9 (C14), 51.0 (C6), 8.0 (C1), 7.0 (C2) – Peak 7 obscured by DMSO peak

HRMS (ESI+): found $[M + H]^+$ 363.1819, $C_{21}H_{23}N_4O_2^+$ required 363.1821.

5.2.4.4. Benzyl (S)-(2-phenyl-1-(3-(4-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-5-yl)ethyl)carbamate (103)



Following General Procedure 4: ethyl 4-(trifluoromethyl)benzimidate **79** (0.84 g, 3.86 mmol) and benzyl (*S*)-(1-hydrazinyl-1-oxo-3-phenylpropan-2-yl)carbamate **52** (1.01 g, 3.22 mmol) in ethanol (7 mL), followed by acetic acid (3.5 mL) were used. The crude product was purified by flash column chromatography eluting with 40% ethyl acetate in 40-60 petroleum ether to yield the title compound **103** as a white solid (1.27 g, 2.73 mmol, 85%).

R_f = 0.70 (40% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -2.3 (c = 0.4 in CH_3OH)

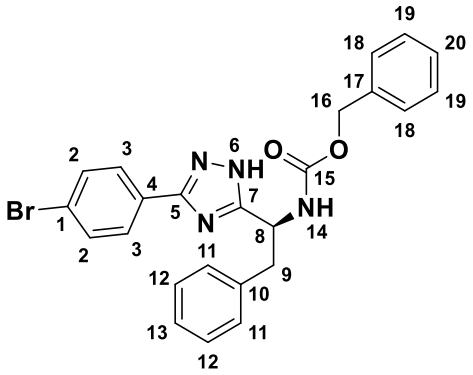
IR ν_{max} = 3250 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1698 (s, C=O), 1529 (m, C=C), 1439 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 14.03 - 14.43 (1H, m, H7), 8.21 (2H, d, *J* = 8.0 Hz, H4), 8.03 (1H, br s, H15), 7.86 (2H, d, *J* = 8.0 Hz, H3), 7.23 - 7.36 (9H, m, H12, 13, 19, 20 & 21), 7.18 - 7.23 (1H, m, H14), 5.02 (1H, m, H9), 5.02 (1H, d, *J* = 16.0 Hz, H17a), 4.95 (1H, d, *J* = 16.0 Hz, H17b), 3.30 (1H, dd, *J* = 13.7, 5.4 Hz, H10a), 3.11 (1H, dd, *J* = 13.7, 9.7 Hz, H10b)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 159.7 (C6), 158.6 (C8), 155.8 (C16), 137.1 (C11), 136.1 (C18), 135.3 (C5), 129.3 (C13), 128.4, 128.3, 127.8 (C12, 19, 21), 127.5 (C20), 126.8 (C2), 126.5 (C4), 125.9 (C3), 125.4 (C14), 123.2 (C1), 65.4 (C17), 49.7 (C9), 38.9 (C10)

HRMS (ESI+): found $[M + H]^+$ 467.1690, $C_{25}H_{22}F_3N_4O_2^+$ required 467.1695.

5.2.4.5. Benzyl (S)-(1-(3-(4-bromophenyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (104)



Following General Procedure 4: ethyl 4-bromobenzimidate **80** (0.86 g, 3.77 mmol) and benzyl (*S*)-(1-hydrazinyl-1-oxo-3-phenylpropan-2-yl)carbamate **52** (0.99 g, 3.14 mmol) in ethanol (7 mL), followed by acetic acid (3.5 mL) were used. The crude product was purified by flash column chromatography eluting with 40% ethyl acetate in 40-60 petroleum ether to yield the title compound **104** as a white solid (1.36 g, 2.86 mmol, 91%).

R_f = 0.66 (40% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +1.7 (c = 0.5 in CH_3OH)

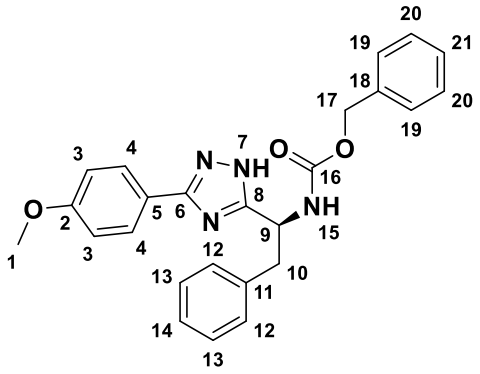
IR ν_{max} = 3250 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1699 (m, C=O), 1533 (m, C=C), 1406 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 14.02 (1H, br s, H6), 8.03 (1H, d, *J* = 6.7 Hz, H14), 7.96 - 7.92 (2H, m, H3), 7.63 - 7.79 (2H, m, H2), 7.17 - 7.37 (10H, m, H11, 12, 13, 18, 19 & 20), 4.87 - 5.07 (3H, m, H8 & 16), 3.28 (1H, m, *J* = 18.3 Hz, H9a), 3.11 (1H, m, *J* = 18.3 Hz, H9b)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 160.5 (C5), 158.7 (C7), 156.2 (C15), 138.0 (C10), 137.4 (C17), 132.2 (C2), 131.1 (C4), 129.7 (C12), 128.7 (C19), 128.6 (C11), 128.2 (C20), 128.1 (C3), 127.9 (C18), 126.9 (C13), 122.6 (C1), 65.4 (C16), 49.6 (C8), 38.9 (C9)

HRMS (ESI+): found $[M + H]^+$ 477.0919, $C_{24}H_{22}BrN_4O_2^+$ required 477.0926.

5.2.4.6. Benzyl (S)-(1-(3-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (105)



Following General Procedure 4: ethyl 4-methoxybenzimidate **81** (0.75 g, 4.20 mmol) and benzyl (*S*)-(1-hydrazinyl-1-oxo-3-phenylpropan-2-yl)carbamate **52** (1.10 g, 3.50 mmol) in ethanol (9 mL), followed by acetic acid (4.5 mL) were used. The crude product was purified by flash column chromatography eluting with 50% ethyl acetate in 40-60 petroleum ether to yield the title compound **105** as a white solid (1.31 g, 3.05 mmol, 87%).

R_f = 0.52 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +4.7 (c = 0.5 in CH_3OH)

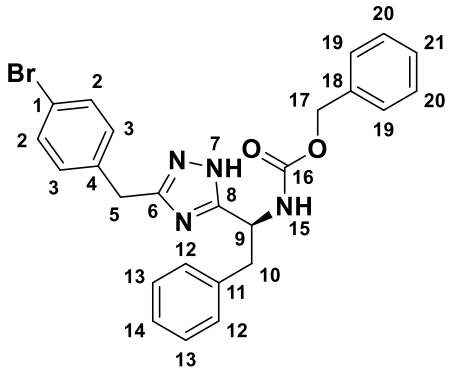
IR ν_{max} = 3220 (w, br, N-H), 2988 (s, C-H), 2901 (s, C-H), 1692 (s, C=O), 1614 (m, C=C), 1583 (w, C=C), 1496 (m, C=C)

^{1}H NMR (400 MHz, d_6-DMSO): δ_H = 7.89 (2H, d, *J* = 8.5 Hz, H4), 7.29 (3H, dd, *J* = 5.2, 1.8 Hz, H20 & 21), 7.20 - 7.25 (2H, m, H12), 7.15 - 7.19 (3H, m, H13 & 14), 7.09 (2H, d, *J* = 5.2 Hz, H19), 6.90 (2H, d, *J* = 8.5 Hz, H3), 6.31 (1H, d, *J* = 7.4 Hz, H15), 5.29 (1H, q, *J* = 7.4 Hz, H9), 5.09 (1H, d, *J* = 12.5 Hz, H17a), 4.96 (1H, d, *J* = 12.2 Hz, H17b), 3.83 (3H, s, H1), 3.30 (1H, dd, *J* = 13.7, 6.7 Hz, H10a), 3.24 (1H, dd, *J* = 13.7, 7.9 Hz, H10b)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 160.9, 158.9 (C2 & 6), 156.3 (C8), 136.5 (C11), 136.1 (C18), 129.3 (C13), 128.4, 128.4 (C12 & 20), 128.0 (C19), 127.8 (C3), 126.7 (C14), 121.4 (C5), 114.2 (C4), 66.9 (C17) 55.3 (C1), 50.2 (C9), 40.5 (C10)

HRMS (ESI+): found $[M + H]^+$ 429.1921, $C_{25}H_{25}N_4O_3^+$ required 429.1927.

5.2.4.7. Benzyl (S)-(1-(3-(4-bromobenzyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (106)



Following General Procedure 4: ethyl 2-(4-bromophenyl)acetimidate **82** (0.89 g, 3.67 mmol) and benzyl (*S*)-(1-hydrazinyl-1-oxo-3-phenylpropan-2-yl)carbamate **52** (0.96 g, 3.06 mmol) in ethanol (7 mL), followed by acetic acid (3.5 mL) were used. The crude product was purified by flash column chromatography eluting with 40% ethyl acetate in 40-60 petroleum ether to yield the title compound **106** as a white solid (0.78 g, 1.58 mmol, 52%).

$\mathbf{R_f}$ = 0.32 (40% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -4.7 (c = 0.4 in CH_3OH)

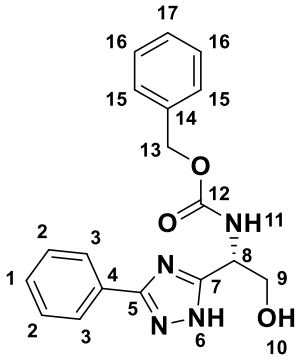
IR: ν_{max} = 3337 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1682 (m, C=O), 1522 (m, C=C), 1488 (m, C=C), 1446 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 13.57 (1H, br s, H7), 7.65 - 7.96 (1H, m, H15), 7.44 - 7.57 (2H, m, H2), 7.31 (2H, m, H19/20), 7.15 - 7.26 (10H, m, H3, H12, 13, 14, 19/20 & 21), 4.88 - 5.04 (2H, m, H17), 4.85 (1H, m, *J* = 7.3 Hz, H9), 3.85 - 4.14 (2H, m, H5), 3.15 (1H, d, *J* = 12.5 Hz, H10a), 2.99 (1H, d, *J* = 12.5 Hz, H10b)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 163.9, (C8), 161.6 (C6), 155.6 (C15), 138.4 (C11), 137.2 (C18), 136.4 (C4), 131.4 (C2), 131.1 (C3), 130.9 (C13), 129.2, 128.3, 128.0 (C12, 20 & 21), 127.6 (C19), 126.1 (C14), 119.8 (C1), 119.3 (C1), 65.3 (C17), 50.9 (C9), 33.4 (C10), 31.3 (C5)

HRMS (ESI+): found $[M + H]^+$ 491.1071, $C_{25}H_{24}BrN_4O_2^+$ required 491.1083.

5.2.4.8. Benzyl (S)-(2-hydroxy-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate (107)



Following General Procedure 4: ethyl benzimidate **53** (1.62 g, 10.9 mmol) and benzyl (*S*)-(1-hydrazinyl-3-methyl-1-oxobutan-2-yl)carbamate **95** (2.30 g, 9.08 mmol) in ethanol (7 mL), followed by acetic acid (3.5 mL) were used. The crude product was purified by flash column chromatography eluting with 50% ethyl acetate in heptane to yield the title compound **107** as a white solid (2.03 g, 6.00 mmol, 66%).

$\mathbf{R_f}$ = 0.57 (50% EtOAc in heptane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -44.8 (c = 0.2 in CH_3OH)

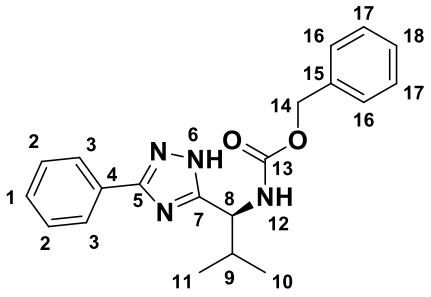
IR ν_{max} = 3397 (w, O-H), 3254 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1678 (s, C=O), 1519 (s, C=C), 1470 (m, C=C), 1444 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 14.00 (1H, br s, H6), 7.96 (2H, d, *J*=7.0 Hz, H3), 7.63 (1H, br s, H11), 7.44 - 7.51 (2H, m, H2), 7.42 (1H, d, *J* = 7.0 Hz, H1), 7.32 - 7.39 (4H, m, H15 & 16), 7.27 - 7.32 (1H, m, H17), 5.06 (1H, d, *J* = 12.3 Hz, H13a), 5.02 (1H, d, *J* = 12.3 Hz, H13b), 4.79 (1H, q, *J* = 6.7 Hz, H8), 3.80 (1H, dd, *J* = 10.5, 5.6 Hz, H9a), 3.69 (1H, dd, *J* = 10.5, 7.2 Hz, H9b)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 164.2, 164.1 (C5 & 6), 156.4 (C12), 137.5, 137.5 (C4 & 14), 129.3, 129.2 (C1 & 2), 128.8, 128.3, 128.2 (C15, 16 & 17), 126.3 (C3), 66.0 (C13), 63.0 (C9), 53.1 (C8)

HRMS (ESI+): found $[M + H]^+$ 339.1457, $C_{18}H_{19}N_4O_3^+$ required 339.1457.

5.2.4.9. Benzyl (S)-(2-methyl-1-(3-phenyl-1H-1,2,4-triazol-5-yl)propyl)carbamate (108)



Following General Procedure 4: ethyl benzimidate **53** (1.55 g, 10.4 mmol) and benzyl (*S*)-(1-hydrazinyl-3-methyl-1-oxobutan-2-yl)carbamate **96** (2.30 g, 8.67 mmol) in ethanol (7 mL), followed by acetic acid (3.5 mL) were used. The crude product was purified by flash column chromatography eluting with 40% ethyl acetate in 40-60 petroleum ether to yield the title compound **108** as a white solid (2.48 g, 7.08 mmol, 82%).

R_f = 0.52 (40% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -62.2 (c = 0.4 in CH_3OH)

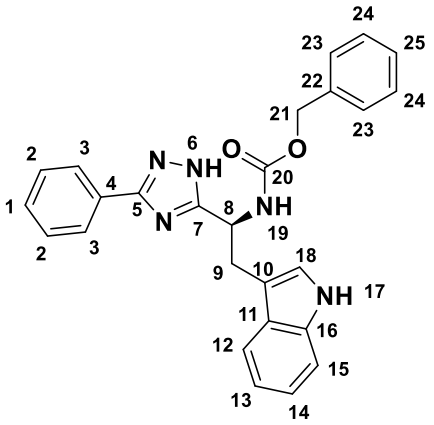
IR ν_{max} = 3250 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1679 (s, C=O), 1552 (m, C=C), 1496 (m, C=C), 1452 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.99 (2H, br s, H3), 7.38 - 7.48 (3H, m, H1 & 2), 7.27 - 7.35 (5H, m, H16, 17 & 18), 6.13 (1H, d, *J* = 8.2 Hz, H12), 5.16 (1H, d, *J* = 12.5 Hz, H14a), 5.07 (1H, d, *J* = 12.5 Hz, H14b), 4.81 (1H, t, *J* = 8.2 Hz, H8), 2.34 (1H, dd, *J* = 8.2, 6.7 Hz, H9), 0.99 (3H, d, *J* = 6.7 Hz, H10/11), 0.91 (3H, d, *J* = 6.7 Hz, H10/11)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 160.1 (C7), 159.8 (C5), 156.7 (C13), 136.1 (C15), 129.8 (C1), 129.4 (C4), 128.8 (C2), 128.5 (C18), 128.2 (C16), 128.0 (C17), 126.5 (C3), 67.2 (C14), 54.5 (C8), 32.3 (C9), 19.2, 18.4 (C10 & 11)

HRMS (ESI+): found $[M + H]^+$ 351.1813, $C_{20}H_{23}N_4O_2^+$ required 351.1816.

5.2.4.10. Benzyl (S)-(2-(1H-indol-3-yl)-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate (109)



Following General Procedure 4: ethyl benzimidate **53** (0.51 g, 3.41 mmol) and benzyl (*S*)-(1-hydrazinyl-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate **97** (1.00 g, 2.84 mmol) in ethanol (5 mL), followed by acetic acid (3 mL) were used. The crude product was purified by flash column chromatography eluting with 50% ethyl acetatein heptane to yield the title compound **109** as a yellow solid (0.91 g, 2.09 mmol, 74%).

R_f = 0.48 (50% EtOAc in heptane)

$[\alpha]_D^{20}$ = +9.4 (c = 0.4 in CH_3OH)

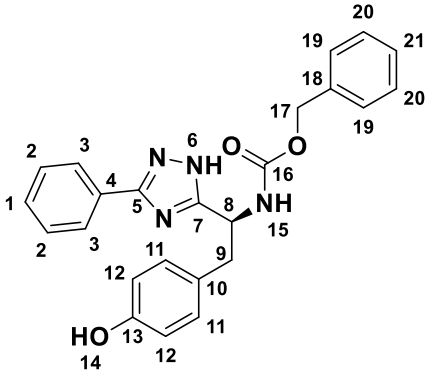
IR ν_{max} = 3258 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1669 (s, C=O), 1614 (m, C=C), 1515 (s, C=C), 1475 (m, C=C), 1444 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 13.90 (1H, br s, H6), 10.79 (1H, br s, H17), 8.00 (2H, d, *J* = 7.3 Hz, H3), 7.58 (1H, d, *J* = 7.5 Hz, H12), 7.40 - 7.53 (3H, m, H1 & 2), 7.30 - 7.34 (3H, m, H15 & 23/24), 7.25 - 7.29 (3H, m, H23/24 & 25), 7.08 (1H, d, *J* = 1.8 Hz, H18), 7.05 (1H, t, *J* = 7.5 Hz, H14), 6.96 (1H, t, *J* = 7.5 Hz, H13), 5.03 (1H, d, *J* = 6.4 Hz, H8), 4.93 (2H, s, H22), 3.35 - 3.45 (1H, m, H9a), 3.18 - 3.28 (1H, m, H9b)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 161.8 (C5), 161.3 (C7), 156.2 (C20), 137.5 (C22), 136.5 (C16), 132.0 (C4), 129.2, 128.8 (C1 & 2), 128.1, 127.9, 127.7 (C23, 24 & 25), 127.2 (C11), 126.3 (C3), 124.2 (C18), 121.3 (C14), 118.8, 118.7 (C12 & 13), 111.8 (C15), 110.3 (C10) 79.4 (C21), 65.7 (C8), peak for C9 obscured by DMSO peak.

HRMS (ESI+): found $[M + H]^+$ 438.1911, $C_{26}H_{24}N_5O_2^+$ required 438.1930.

5.2.4.11. Benzyl (S)-(2-(4-hydroxyphenyl)-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate (110)



Following General Procedure 4: ethyl benzimidate **53** (0.65 g, 4.34 mmol) and benzyl (*S*)-(1-hydrazinyl-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamate **98** (1.19 g, 3.62 mmol) in ethanol (8 mL), followed by acetic acid (3.6 mL) were used. The crude product was purified by flash column chromatography eluting with 50% ethyl acetate in 40-60 petroleum ether to yield the title compound **110** as a yellow solid (1.25 g, 3.01 mmol, 83%).

R_f = 0.73 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +9.5 (c = 0.4 in CH_3OH)

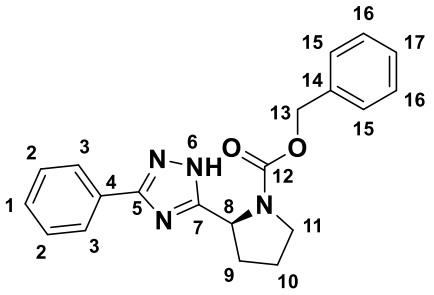
IRν_{max} = 3411 (m, O-H), 3322 (w, N-H), 3254 (m, N-H), 2971 (s, C-H), 2901 (s, C-H), 1699 (s, C=O), 1615 (w, C=C), 1533 (s, C=C), 1469 (m, C=C), 1454 (m, C=C), 1443 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 9.30 (1H, br s, H14), 7.96 (2H, d, *J* = 7.5, H3), 7.82 (1H, br s, H15), 7.42 - 7.47 (3H, m, H1 & 2), 7.25 - 7.32 (3H, m, H20 & 21), 7.22 (1H, d, *J* = 7.0 Hz, H19), 7.01 (1H, d, *J* = 8.5 Hz, H11), 6.62 (1H, d, *J* = 8.5 Hz, H12), 4.98 (1H, d, *J* = 13.0 Hz, H17a), 4.92 (1H, d, *J* = 13.0 Hz, H17b), 4.86 (1H, dd, *J* = 9.9, 6.0 Hz, H8), 3.12 (1H, dd, *J* = 13.6, 6.0 Hz, H9a), 2.93 (1H, dd, *J* = 13.6, 9.9 Hz, H9b)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 172.5 (C7), 170.8 (C5), 156.3, 156.2 (C13 & 16), 137.6 (C18), 130.6 (C11), 129.3 (C1), 129.8 (C2), 128.7 (C20), 128.1 (C21), 127.8 (C19), 127.0 (C4), 126.3 (C3), 115.4 (C12), 65.6 (C17), 60.2 (C8), C9 hidden by DMSO peak.

HRMS (ESI+): found $[M + H]^+$ 415.1758, $C_{24}H_{23}N_4O_3^+$ required 415.1770.

5.2.4.12. Benzyl (S)-2-(3-phenyl-1H-1,2,4-triazol-5-yl)pyrrolidine-1-carboxylate (111)



Following General Procedure 4: ethyl benzimidate **53** (0.61 g, 4.10 mmol) and benzyl (*S*)-2-(hydrazinecarbonyl)pyrrolidine-1-carboxylate **99** (0.90 g, 3.42 mmol) in ethanol (8 mL), followed by acetic acid (4 mL) were used. The crude product was purified by flash column chromatography eluting with 50% ethyl acetate in 40-60 petroleum ether to yield the title compound **111** as a white solid (0.83 g, 2.39 mmol, 70%).

R_f = 0.36 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -73.5 (c = 0.4 in CH_3OH)

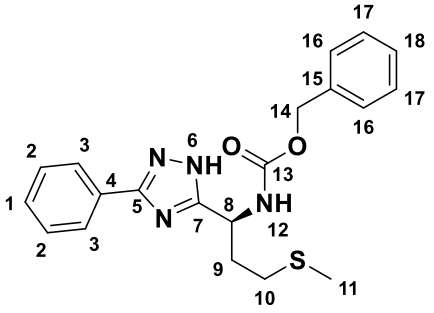
IR ν_{max} = 3062 (m, C-H), 1670 (s, br, C=O), 1555 (w, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 13.75 - 14.32 (1H, m, H6), 7.99 (2H, br s, H3), 7.28 - 7.59 (5H, m, H1, 2, 15/16 &17), 6.99 - 7.19 (2H, m, H15/16), 4.85 - 5.15 (3H, m, H8 & 13), 3.55 - 3.70 (1H, m, H11a), 3.48 (1H, t, *J* = 7.9 Hz, H11b), 2.19 - 2.40 (1H, m, H9a), 1.83 - 2.11 (3H, m, H9b & 10)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 161.4 (C7), 159.6, 159.3 (C5), 154.6, 154.2 (C12), 137.6, 137.3 (C14), 132.0, 131.7 (C4), 130.5 (C1), 129.5 129.3, 129.1, 128.8, 128.7, 128.5, 127.9, 127.1 (C2, 15, 16 & 17), 126.4, 126.2 (C3), 66.5, 66.2 (C13), 54.5,54.1 (C8), 47.4, 46.8 (C11), 33.3, 32.3 (C9), 24.2, 23.4 (C10) - mixture of rotamers.

HRMS (ESI+): found $[M + H]^+$ 349.1659, $C_{20}H_{21}N_4O_2^+$ required 349.1665.

5.2.4.13. Benzyl (S)-(3-(methylthio)-1-(3-phenyl-1H-1,2,4-triazol-5-yl)propyl)carbamate (112)



Following General Procedure 4: ethyl benzimidate **53** (181 mg, 1.21 mmol) and benzyl (*S*)-(1-hydrazinyl-4-(methylthio)-1-oxobutan-2-yl)carbamate **100** (300 mg, 1.01 mmol) in ethanol (2 mL), followed by acetic acid (1 mL) were used. The crude product was purified by flash column chromatography eluting with 50% ethyl acetate in 40-60 petroleum ether to yield the title compound **112** as a white solid (370 mg, 0.97 mmol, 98%).

R_f = 0.71 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -40.2 (c = 0.6 in CH_3OH)

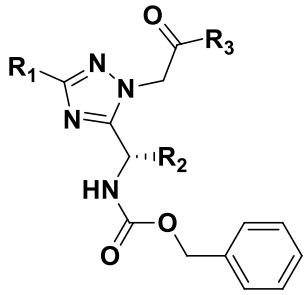
IR ν_{max} = 3269 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1691 (m, C=O), 1532 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.00 (1H, d, *J* = 7.0 Hz, H3), 7.39 - 7.48 (3H, m, H 1 & 2), 7.28 - 7.38 (5H, m, H 16, 17 & 18), 5.08 - 5.17 (3H, m, H8 & 14), 2.51 - 2.64 (2H, m, H10), 2.33 (1H, dt, *J* = 14.3 6.4 Hz, H9a), 2.24 (1H, dt, *J* = 14.3, 7.5 Hz, H9b), 2.10 (3H, s, H11)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 160.6 (C7), 160.0 (C5), 156.2 (C13), 136.2 (C18), 129.8 (C1), 128.7 (C4), 128.6 (C2), 128.8, 128.2, 128.2 (C16, 17 & 18), 126.4 (C3), 67.1 (C14), 48.2 (C8), 33.8 (C9), 30.1 (C10), 15.4 (C11)

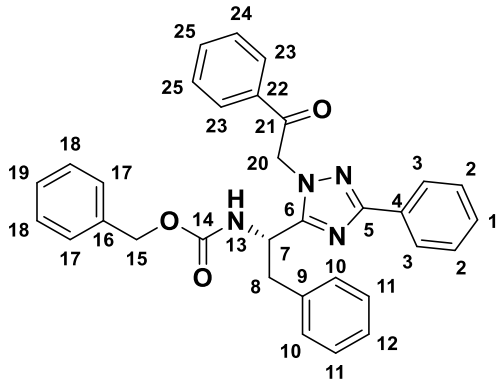
HRMS (ESI+): found $[M + H]^+$ 383.1542, $C_{20}H_{23}N_4O_2S^+$ required 383.1542.

5.2.5. General procedure for the alkylation of the Heterocycle



General Procedure 5: A solution of the required triazole carbamate (1.0 eq.), the required α-bromoketone (1.2 eq.) and potassium carbonate (1.0 eq.) in DMF or acetone (0.2 M) was stirred at room temperature until complete. The reaction was quenched with water and extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed brine (10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure. The resultant crude compound was purified by flash column chromatography on silica to yield the title compound.

5.2.5.1. Benzyl ((1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)methyl)carbamate (56)



Following General Procedure 5: benzyl ((3-phenyl-1*H*-1,2,4-triazol-5-yl)methyl)carbamate **54** (500 mg, 1.26 mmol), 2-bromoacetophenone **55** (300 mg, 1.51 mmol) and potassium carbonate (174 mg, 1.26 mmol) in DMF (3 mL) were used. The crude product was purified by flash column chromatography eluting with 50% ethyl acetate in heptane to yield the title compound **56** as a yellow white solid (521 mg, 1.01 mmol, 80%).

$\mathbf{R_f}$ = 0.65 (50% EtOAc in heptane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +8.5 (c = 0.4 in $CHCl_3$)

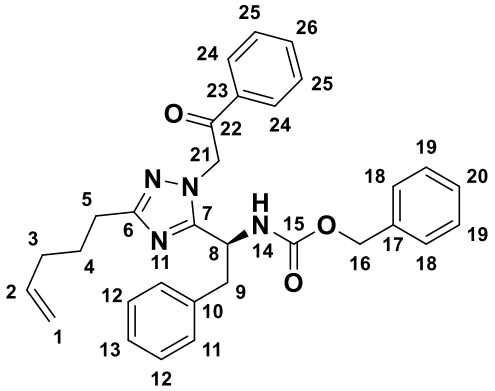
IR ν_{max} = 3209 (w, N-H), 2936 (w, C-H), 1771 (w, C=O), 1711 (s, C=O), 1539 (m, C=N)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.10 (2H, dd, *J* = 8.1, 1.4 Hz, H3), 7.92 (2H, d, *J* = 7.5 Hz, H23), 7.65 (1H, tt, *J* = 7.5, 1.2 Hz, H25), 7.52 (2H, t, *J* = 7.5 Hz, H24), 7.38 - 7.47 (3H, m, H1 & 2), 7.25 - 7.34 (6H, m, H10, 12, 17 & 19), 7.18 - 7.24 (4H, m, H11 & 18), 5.73 (1H, d, *J* = 8.2 Hz, H13), 5.66 (1H, d, *J* = 18.0 Hz, H20a), 5.37 (1H, d, *J* = 18.0 Hz, H20b), 5.01 (1H, d, *J* = 12.5 Hz, H15a), 4.96 (1H, d, *J* = 8.2 Hz, H7), 4.92 (1H, d, *J* = 12.5 Hz, H15b), 3.41 (2H, d, *J* = 7.3 Hz, H8)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 191.1 (C21), 161.4 (C5), 157.3 (C6), 156.0 (C14), 136.7 (C9), 136.0 (C16), 134.3 (C25), 134.1 (C22), 130.8 (C4) 129.4 (C1), 129.3 (C11), 129.0 (C24), 128.7 (C12), 128.6 (C17), 128.5 (C19), 128.3 (C2), 128.2 (C23) 127.8 (C18), 127.0 (C10), 126.5 (C3), 67.0 (C15), 54.5 (C20), 48.7 (C7), 40.5 (C8)

HRMS (ESI+): found $[M + H]^+$ 517.2232, $C_{32}H_{29}N_4O_3^+$ required 517.2234.

5.2.5.2. Benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-3-(pent-4-en-1-yl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (119)



Following General Procedure 5: benzyl (*S*)-(1-(3-(pent-4-en-1-yl)-1*H*-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **101** (146 mg, 0.370 mmol), 2-bromoacetophenone **55** (92.0 mg, 0.460 mmol) and potassium carbonate (52.0 mg, 0.370 mmol) in DMF (1 mL) were used. The crude product was purified by flash column chromatography eluting with 0-60% ethyl acetate in 40-60 petroleum ether to yield the title compound **119** as a yellow liquid (123 mg, 0.240 mmol, 65%).

R_f = 0.42 (40% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -15.7 (c = 0.1 in $CHCl_3$)

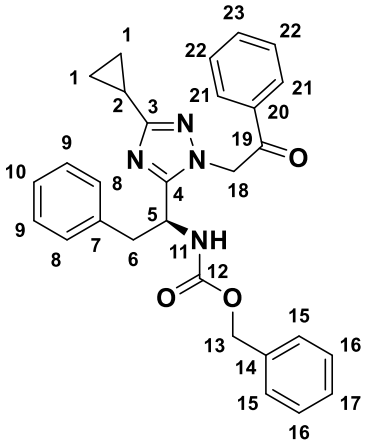
IR: ν_{max} = 3367 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1699 (s, C=O), 1597 (w, C=C), 1496 (m, C=C), 1450 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.97 (2H, d, *J* = 7.9 Hz, H24), 7.63 - 7.72 (1H, m, H26), 7.49 - 7.58 (2H, m, H25), 7.28 - 7.40 (5H, m, H18, 19 & 20), 7.14 - 7.23 (3H, m, H11 & 13), 6.98 - 7.08 (2H, m, H12), 5.71 - 5.84 (1H, m, H2), 5.51 (1H, d, *J* = 7.9 Hz, H16a), 5.46 (2H, s, H21), 5.17 - 5.26 (1H, m, H16b), 4.92 - 5.15 (3H, m, H1 & 8), 3.25 - 3.32 (1H, m, H9a), 3.17 - 3.24 (1H, m, H9b), 2.60 (2H, t, *J* = 7.4 Hz, H5), 2.12 (2H, q, *J* = 7.4 Hz, H3), 1.87 (2H, quin, *J*=7.4 Hz, H4)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 190.5 (C22), 162.3 (C7), 157.9 (C6), 155.6 (C15), 137.6 (C2), 136.6 (C10), 136.6 (C17), 134.4 (C26), 134.1 (C23), 129.7 (C12), 129.1 (C25), 128.5, 128.4, 128.4 (C18, 19 & 20), 128.1 (C24), 128.0 (C11), 126.5 (C13), 115.6 (C1), 66.6 (C16), 54.1 (C21), 50.8 (C8), 41.0 (C9), 33.0 (C3), 26.5 (C4), 25.1 (C5)

HRMS (ESI+): found $[M + H]^+$ 509.2547, $C_{31}H_{33}N_4O_3^+$ required 509.2553.

5.2.5.3. Benzyl (S)-(1-(3-cyclopropyl-1-(2-oxo-2-phenylethyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (120)



Following General Procedure 5: benzyl (*S*)-(1-(3-cyclopropyl-1*H*-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **102** (763 mg, 2.11 mmol), 2-bromoacetophenone **55** (503 mg, 2.53 mmol) and potassium carbonate (291 mg, 2.11 mmol) in acetone (2 mL) were used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in 40-60 petroleum ether to yield the title compound **120** as a yellow-white solid (540 mg, 1.12 mmol, 53%).

R_f = 0.26 (30% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +10.6 (c = 0.3 in $CHCl_3$)

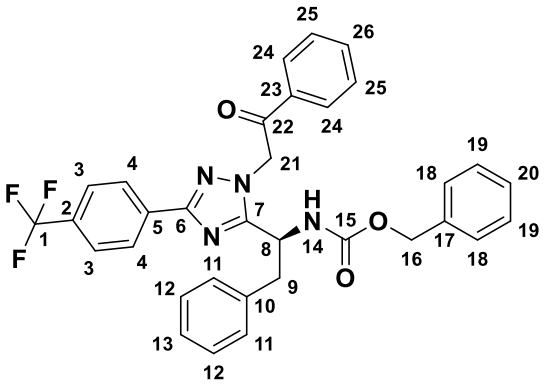
IR ν_{max} = 2902 (s, C-H), 2851 (m, C-H), 1711 (s, C=O), 1604 (w, C=C), 1496 (m, C=C), 1453 (m, C=C)

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.91 (2H, d, *J* = 7.6 Hz, H21), 7.66 (1H, t, *J* = 7.6 Hz, H23), 7.52 (2H, t, *J* = 7.6 Hz, H22), 7.30 - 7.37 (4H, m, H15 & 16), 7.21 - 7.28 (4H, m, H9, 10 & 17), 7.15 (2H, d, *J* = 5.6 Hz, H8), 5.46 - 5.58 (2H, m, H11 & 18a), 5.25 (1H, d, *J* = 17.9 Hz, H18b), 5.00 (1H, d, *J* = 12.2 Hz H13a), 4.93 (1H, d, *J* = 12.2 Hz, H13b), 4.86 (1H, q, *J* = 7.6 Hz, H5), 3.29 (2H, d, *J* = 7.6 Hz, H6), 1.99 - 2.08 (1H, m, H2), 0.95 - 1.01 (4H, m, H1)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 191.2 (C19), 165.2 (C4), 156.4 (C12), 155.8 (C3), 136.6 (C7), 136.0 (C14), 134.2, 134.1 (C20 & 23), 129.3 (C22), 128.9 (C9), 128.7 (C21), 128.6 (C16), 128.4 (C8), 128.1 (C17), 127.7 (C15), 126.9 (C10), 66.9 (C13), 54.0 (C18), 48.4 (C5), 40.4 (C6), 8.9 (C2), 7.8 (C1)

HRMS (ESI+): found $[M + H]^+$ 481.2237, $C_{29}H_{29}N_4O_3^+$ required 481.2240.

5.2.5.4. Benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-3-(4-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (121)



Following General Procedure 5: benzyl (*S*)-(2-phenyl-1-(3-(4-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-5-yl)ethyl)carbamate **103** (185 mg, 0.400 mmol), 2-bromoacetophenone **55** (95.0 mg, 0.480 mmol) and potassium carbonate (55.0 mg, 0.400 mmol) in acetone (4 mL) were used. The crude product was purified by flash column chromatography eluting with 0-40% ethyl acetate in 40-60 petroleum ether to yield the title compound **121** as a white solid (169 mg, 0.290 mmol, 73%).

R_f = 0.45 (20% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +4.9 (c = 0.4 in $CHCl_3$)

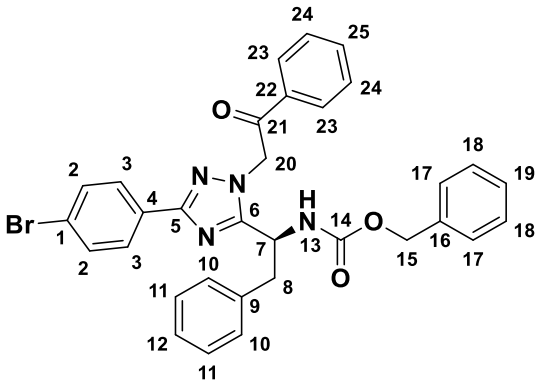
IR: ν_{max} = 3314 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1697 (s, C=O), 1614 (w, C=C), 1533 (m, C=C), 1478 (m, C=C), 1435 (m, C=C), 1406 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.21 (2H, d, *J* = 8.0 Hz, H4), 8.11 (1H, d, *J* = 8.9 Hz, H14), 8.01 - 8.06 (2H, m, H24), 7.85 (2H, d, *J* = 8.0 Hz, H3), 7.69 - 7.75 (1H, m, H26), 7.55 - 7.62 (2H, m, H25), 7.16 - 7.32 (8H, m, H11, 12, 13, 19 & 20), 7.07 (2H, dd, *J* = 7.3, 2.1 Hz, H18), 6.20 (1H, d, *J* = 18.3 Hz, H21a), 6.03 (1H, d, *J* = 18.3 Hz, H21b), 5.05 (1H, ddd, *J* = 10.1, 8.9, 4.9 Hz, H8), 4.77 (1H, d, *J* = 12.8 Hz, H16a), 4.67 (1H, d, *J* = 12.8 Hz, H16b), 3.28 (1H, dd, *J* = 14.0, 10.1 Hz, H9a), 3.24 (1H, dd, *J* = 14.0, 4.9 Hz, H9b)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 192.7 (C22), 159.2 (C7), 159.0 (C6), 156.3 (C15), 138.0 (C10), 137.2 (C17), 135.1 (C5), 134.7, 134.6 (C23 & 26), 129.8 (C25), 129.5 (C12), 128.7 (C24), 128.5, 128.1 (C19 & 20), 127.8 (C13), 126.9 (C18), 126.8 (C4), 126.4 (C11), 126.3 (C3), 123.6 (C2), 121.4 (C1), 65.8 (C16), 55.7 (C21), 48.1 (C8), 38.5 (C9)

HRMS (ESI+): found $[M + H]^+$ 585.2124, $C_{33}H_{28}F_3N_4O_3^+$ required 585.2114.

5.2.5.5. Benzyl (S)-(1-(3-(4-bromophenyl)-1-(2-oxo-2-phenylethyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (122)



Following General Procedure 5: benzyl (*S*)-(1-(3-(4-bromophenyl)-1*H*-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **104** (216 mg, 0.260 mmol), 2-bromoacetophenone **55** (63.0 mg, 0.320 mmol) and potassium carbonate (36.0 mg, 0.260 mmol) in acetone (2.6 mL) were used. The crude product was purified by flash column chromatography eluting with 0-40% ethyl acetate in 40-60 petroleum ether to yield the title compound **122** as a white solid (128 mg, 0.210 mmol, 83%).

R_f = 0.54 (20% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +2.7 (c = 0.4 in $CHCl_3$)

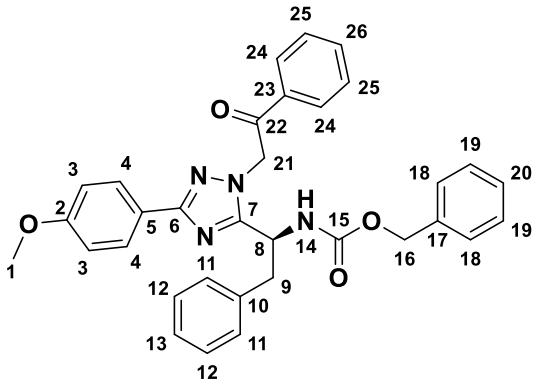
IR: ν_{max} = 3249 (w, N-H), 2988 (s, C-H), 2902 (s, C-H), 1697 (s, C=O), 1528 (m, C=C), 1406 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.11 (1H, d, *J* = 9.0 Hz, H13), 8.05 (2H, d, *J* = 7.6 Hz, H23), 7.96 (2H, d, *J* = 8.5 Hz, H3), 7.72 - 7.76 (1H, m, H25), 7.70 (2H, d, *J* = 8.5 Hz, H2), 7.58 - 7.63 (2H, m, H24), 7.18 - 7.34 (8H, m, H10, 11, 12, 18 & 19), 7.07 - 7.13 (2H, m, H17), 6.18 (1H, d, *J* = 18.6 Hz, H20a), 6.01 (1H, d, *J* = 18.6 Hz, H20b), 5.04 (1H, td, *J* = 9.0, 5.2 Hz, H7), 4.78 (1H, d, *J* = 12.5 Hz, H15a), 4.69 (1H, d, *J* = 12.5 Hz, H15b), 3.29 (1H, dd, *J* = 14.0, 9.0 Hz, H8a), 3.24 (1H, dd, *J* = 14.0, 5.2 Hz, H8b)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 192.7 (C21), 159.3 (C5), 158.9 (C7), 156.3 (C14), 138.1 (C9), 137.2 (C16), 134.6 (C25), 134.6 (C22), 132.3 (C2), 130.5 (C4), 129.8 (C11), 129.4 (C24), 128.7, 128.7 (C10 & 19), 128.6 (C23), 128.2 (C3), 128.1 (C19) 127.8(C17), 126.9 (C12), 122.9 (C1), 65.8 (C15), 55.6 (C20), 48.1 (C7), 38.5 (C8)

HRMS (ESI+): found $[M + H]^+$ 595.1342, $C_{32}H_{28}BrN_4O_3^+$ required 595.1345.

5.2.5.6. Benzyl (S)-(1-(3-(4-methoxyphenyl)-1-(2-oxo-2-phenylethyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (123)



Following General Procedure 5: benzyl (*S*)-(1-(3-(4-methoxyphenyl)-1*H*-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **105** (500 mg, 1.17 mmol), 2-bromoacetophenone **55** (279 mg, 1.40 mmol) and potassium carbonate (162 mg, 1.17 mmol) in DMF (7 mL) were used. The crude product was purified by flash column chromatography eluting with 0-40% ethyl acetate in 40-60 petroleum ether to yield the title compound **123** as a pale yellow solid (494 mg, 0.900 mmol, 77%).

R_f = 0.68 (40% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +2.5 (c = 0.4 in $CHCl_3$)

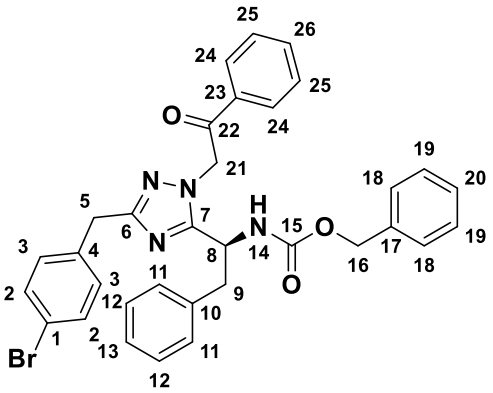
IR: ν_{max} = 3321 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1697 (s, C=O), 1613 (w, C=C), 1534 (m, C=C), 1477 (m, C=C), 1451 (m, C=C), 1434 (m, C=C), 1421 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.08 (1H, d, *J* = 8.5 Hz, H14), 8.04 (2H, dd, *J* = 7.8, 1.2 Hz, H24), 7.90 - 7.95 (2H, m, H4), 7.71 (1H, t, *J* = 7.8 Hz, H26), 7.58 (2H, t, *J* = 7.8 Hz, H25), 7.16 - 7.32 (8H, m, H11 , 12, 13, 19 & 20), 7.08 (2H, dd, *J* = 7.5, 2.0 Hz, H18), 7.02 (2H, dd, *J* = 8.5, 2.0Hz, H3), 6.13 (1H, d, *J* = 18.3 Hz, H21a), 5.95 (1H, d, *J* = 18.3 Hz, H21b), 4.98 (1H, ddd, *J* = 10.1, 8.5, 4.9 Hz, H8), 4.77 (1H, d, *J* = 12.5 Hz, H16a), 4.68 (1H, d, *J* = 12.5 Hz, H16b), 3.80 (1H, s, H1), 3.27 (1H, dd, *J* = 14.0, 10.1 Hz, H9a), 3.22 (1H, dd, *J* = 14.0, 4.9 Hz, H9b)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 192.9 (C22), 160.4, 160.1 (C2 & 6), 158.4 (C7), 156.3 (C15), 138.2 (C10), 137.2 (C17), 134.6, 134.5 (C23 & 26), 129.8 (C12), 129.4 (C25), 128.7 (C11), 128.7 (C19), 128.5 (C24), 128.1 (C20), 127.7 (C18), 127.6 (C3), 126.8 (C13), 124.0 (C5), 114.6 (C4), 65.7 (C16), 55.7 (C1), 55.4 (C21), 48.2 (C8), 38.6 (C9)

HRMS (ESI+): found $[M + H]^+$ 547.2345, $C_{33}H_{31}N_4O_4^+$ required 547.2345.

5.2.5.7. Benzyl (S)-(1-(3-(4-bromobenzyl)-1-(2-oxo-2-phenylethyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (124)



Following General Procedure 5: benzyl (*S*)-(1-(3-(4-bromobenzyl)-1*H*-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **106** (300 mg, 0.610 mmol), 2-bromoacetophenone **55** (128 mg, 0.640 mmol) and potassium carbonate (85.0 mg, 0.610 mmol) in DMF (2.5 mL) were used. The crude product was purified by flash column chromatography eluting with 0-40% ethyl acetate in 40-60 petroleum ether to yield the title compound **124** as a yellow solid (193 mg, 0.320 mmol, 52%).

R_f = 0.43 (30% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +25.0 (c = 0.2 in $CHCl_3$)

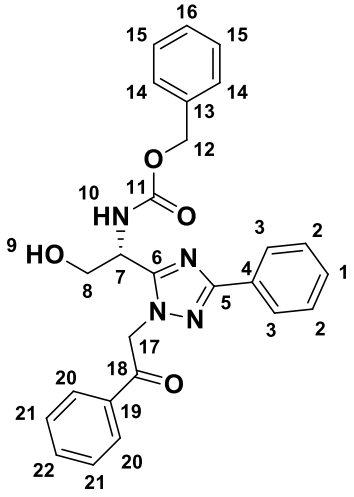
IR: ν_{max} = 3321 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1696 (s, C=O), 1534 (m, C=C), 1479 (m, C=C), 1406 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.01 (2H, d, *J* = 7.5 Hz, H24), 7.71 (1H, t, *J* = 7.5 Hz, H26), 7.57 (2H, t, *J* = 7.5 Hz, H25), 7.49 (2H, d, *J* = 8.2 Hz, H2), 7.14 - 7.31 (11H, m, H3, 11, 13, 14, 18, 19 & 20), 7.05 - 7.11 (2H, m, H12), 6.03 (1H, d, *J* = 18.3 Hz, H21a), 5.84 (1H, d, *J* = 18.3 Hz, H21b), 4.93 (1H, td, *J* = 9.2, 5.6 Hz, H8), 4.77 (1H, d, *J* = 13.0 Hz, H16a), 4.68 (1H, d, *J* = 13.0 Hz, H16b), 3.97 (2H, s, H5), 3.18 (1H, dd, *J* = 14.5, 9.2 Hz, H9a), 3.13 (1H, dd, *J* = 14.5, 5.6 Hz, H9b)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 192.9 (C22), 161.1 (C6), 158.0 (C7), 156.2 (C15), 138.2 (C1), 138.1 (C10), 137.2 (C17), 134.6, 134.5 (C23 & 26), 131.6, 131.5 (C2 & 3), 129.8 (C12), 129.3 (C25), 128.7, 128.6, 128.5 (C11, 19 & 24), 128.1 (C20), 127.7 (C18), 126.8 (C13), 119.9 (C4), 65.7 (C16), 55.1 (C21), 48.1 (C8), 38.6 (C9), 33.8 (C5)

HRMS (ESI+): found $[M + H]^+$ 609.1486, $C_{33}H_{30}BrN_4O_3^+$ required 609.1501.

5.2.5.8. (S)-benzyl 2-hydroxy-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)ethylcarbamate (125)



Following General Procedure 5: benzyl (*S*)-(2-hydroxy-1-(3-phenyl-1*H*-1,2,4-triazol-5-yl)ethyl)carbamate **107** (300 mg, 0.890 mmol), 2-bromoacetophenone **55** (212 mg, 1.07 mmol) and potassium carbonate (123 mg, 0.890 mmol) in acetone (4 mL) were used. The crude product was purified by flash column chromatography eluting with ethyl acetate (0-40%) in 40-60 petroleum ether to yield the title compound **125** as a white solid (220 mg, 0.480 mmol, 55%).

R_f = 0.58 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -23.8 (c = 0.4 in $CHCl_3$)

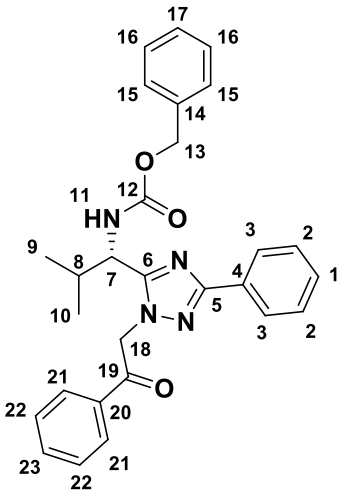
IR: ν_{max} = 3297 (w, br, O-H), 3254 (w, N-H), 2987 (s, C-H), 2901 (s, C-H), 1690 (s, C=O), 1532 (m, C=C), 1446 (m, C=C), 1407 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.06 (2H, dd, *J* = 8.1, 1.7 Hz, H3), 8.01 (2H, d, *J* = 7.8 Hz, H20), 7.67 (1H, t, *J* = 7.8 Hz, H22), 7.55 (2H, t, *J* = 7.8 Hz, H21), 7.38 - 7.45 (3H, m, H1 & 2), 7.30 - 7.36 (3H, m, H15 & 16), 7.27 (2H, dd, *J* = 8.0, 1.8 Hz, H14), 6.07 (1H, d, *J* = 8.0 Hz, H10), 6.07 (1H, d, *J* = 8.9 Hz, H17a), 5.94 (1H, d, *J* = 8.9 Hz, H17b), 5.04 (1H, d, *J* = 12.2 Hz, H12a), 4.91 (1H, d, *J* = 12.2 Hz, H12b), 4.80 (1H, ddd, *J* = 8.0, 3.7, 2.1 Hz,H7), 4.31 (1H, dd, *J* = 11.4, 2.1 Hz, H8a), 3.94 (1H, dd, *J* = 11.4, 3.7 Hz, H8b)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 191.6 (C18), 161.0 (C5), 156.9 (C6), 156.3 (C11), 135.8 (C13), 134.4 (C22), 134.1 (C19), 130.2 (C4), 129.5, 129.4 (C1 & 16), 129.1 (C21), 128.6, 128.5 (C2 & 15), 128.2 (C20) 127.9 (C14), 126.4 (C3) , 67.2 (C12), 64.0 (C8), 55.1 (C17), 46.6 (C7)

HRMS (ESI+): found $[M + H]^+$ 457.1876, $C_{26}H_{25}N_4O_4^+$ required 457.1876.

5.2.5.9. Benzyl (S)-(2-methyl-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)propyl)carbamate (126)



Following General Procedure 5: benzyl (*S*)-(2-methyl-1-(3-phenyl-1*H*-1,2,4-triazol-5-yl)propyl)carbamate **108** (509 mg, 1.45 mmol), 2-bromoacetophenone **55** (347 mg, 1.74 mmol) and potassium carbonate (201 mg, 1.45 mmol) in DMF (3 mL) were used. The crude product was purified by flash column chromatography eluting with 0-40% ethyl acetate in 40-60 petroleum ether to yield the title compound **126** as a white solid (520 mg, 1.14 mmol, 79%).

R_f = 0.50 (30% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$= -62.1 (c = 0.5 in $CHCl_3$)

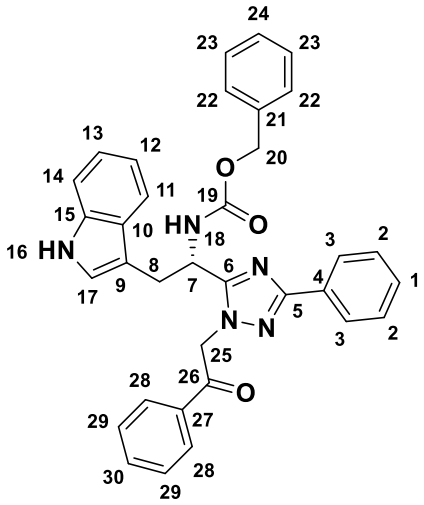
IR: ν_{max} = 3291 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1694 (s, C=O), 1597 (w, C=C), 1540 (m, C=C), 1503 (m, C=C), 1470 (m, C=C), 1445 (m, C=C), 1406 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.06 (2H, dd, *J* = 7.5, 1.5 Hz, H21), 7.99 (3H, dt, *J* = 8.2, 1.2 Hz, H3 & 11), 7.74 (1H, tt, *J* = 7.5, 1.2 Hz, H23), 7.61 (2H, t, *J* = 7.5 Hz, H22), 7.45 - 7.50 (2H, m, H2), 7.42 (1H, t, *J*=7.0 Hz, H1), 7.27 - 7.36 (5H, m, H15, 16 & 17), 6.17 (1H, d, *J* = 18.5 Hz, H18a), 6.08 (1H, d, *J* = 18.5 Hz, H18b), 4.95 (1H, d, *J* = 12.5 Hz, H13a), 4.89 (1H, d, *J* = 12.5 Hz, H13b), 4.53 (1H, t, *J* = 9.2 Hz, H7), 2.33 (1H, dt, *J* = 9.2, 6.7 Hz, H8), 1.00 (3H, d, *J* = 6.7 Hz, H9/10), 0.84 (3H, d, *J* = 6.7 Hz, H9/10)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 192.7 (C19), 160.2 (C5), 158.5 (C6), 156.6 (C12), 137.3 (C16), 134.7, 134.5 (C20 & 23), 131.4 (C4), 129.6 (C1), 129.4, 129.2 (C2 & 22), 128.8, 128.7 (C16 & 21), 128.3 (C17), 128.1 (C15), 126.1 (C3), 66.0 (C13), 55.4 (C18), 52.8 (C7), 31.3 (C8), 20.0, 19.4 (C9 & 10)

HRMS (ESI+): found $[M + H]^+$ 469.2240, $C_{28}H_{29}N_4O_3^+$ required 469.2240.

5.2.5.10. Benzyl (S)-(2-(1H-indol-3-yl)-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate (127)



Following General Procedure 5: benzyl (*S*)-(2-(1*H*-indol-3-yl)-1-(3-phenyl-1*H*-1,2,4-triazol-5-yl)ethyl)carbamate **109** (100 mg, 0.230 mmol), 2-bromoacetophenone **55** (55.0 mg, 0.270 mmol) and potassium carbonate (32.0 mg, 0.230 mmol) in DMF (1 mL) were used. The crude product was purified by flash column chromatography eluting with 0-70% ethyl acetate in 40-60 petroleum ether to yield the title compound **127** as a white solid (103 mg, 0.190 mmol, 81%).

R_f = 0.56 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +39.3 (c = 0.4 in $CHCl_3$)

IR: ν_{max} = 3316 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1698 (s, C=O), 1533 (m, C=C), 1445 (m, C=C), 1408 (m, C=C)

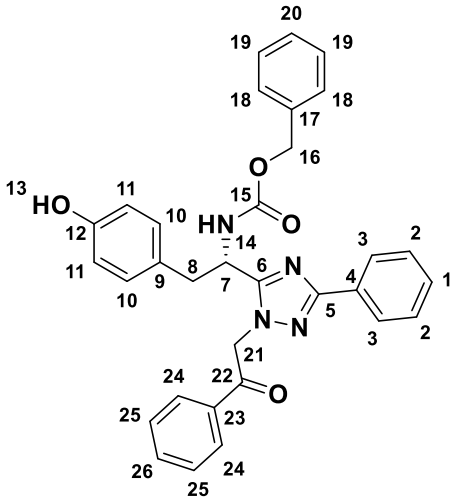
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 10.84 (1H, d, *J* = 2.1 Hz, H16), 8.16 (1H, d, *J* = 8.2 Hz, H18), 8.07 (2H, d, *J* = 7.3 Hz, H28), 8.04 (2H, dt, *J* = 7.3, 1.5 Hz, H3), 7.74 (1H, tt, *J* = 7.3, 1.3 Hz, H30), 7.62 (2H, t, *J* = 7.3 Hz, H29), 7.48 - 7.53 (3H, m, H2 & 11), 7.45 (1H, tt, *J* = 7.3, 1.8 Hz, H1), 7.33 (1H, d, *J* = 7.0 Hz, H14), 7.24 - 7.31 (3H, m, H23 & 24), 7.22 (1H, d, *J* = 2.1 Hz, H17), 7.15 (2H, dd, *J* = 7.6, 1.8 Hz, H22), 7.04 (1H, t, *J* = 7.0 Hz, H13), 6.88 (1H, t, *J* = 7.0 Hz, H12), 6.16 (1H, d, *J* = 18.3 Hz, H25a), 6.00 (1H, d, *J* = 18.3 Hz, H25b), 4.91 (1H, ddd, *J* = 10.1, 8.2, 5.0 Hz, H7), 4.83 (1H, d, *J* = 12.5 Hz, H20a), 4.78 (1H, d, *J* = 12.5 Hz, H20b), 3.43 (1H, dd, *J* = 14.9, 10.1 Hz, H8a), 3.34 (1H, dd, *J* = 14.9, 5.0 Hz, H8b)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C =193.0 (C26), 160.2 (C5), 159.0 (C6), 156.4 (C19), 137.1 (C21), 136.5 (C15), 134.8, 134.4 (C27 & 30), 131.4 (C4), 129.6 (C1), 129.4 (C29), 129.2 (C2), 128.7, 128.7

(C23 & 28), 128.2 (C24), 127.9 (C22), 127.5 (C10), 126.2 (C3), 124.7 (C17), 121.3 (C13), 118.8 (C12), 118.5 (C11), 111.9 (C14), 110.3 (C9), 65.9 (C20), 55.6 (C25), 47.7 (C7), 28.9 (C8)

HRMS (ESI+): found $[M + H]^+$ 556.2332, $C_{34}H_{30}N_5O_3^+$ required 556.2349.

5.2.5.11. Benzyl (S)-(1-(1-(2-(4-hydroxyphenyl)-2-oxoethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (128)



Following General Procedure 5: benzyl (*S*)-(2-(4-hydroxyphenyl)-1-(3-phenyl-1*H*-1,2,4-triazol-5-yl)ethyl)carbamate **110** (131 mg, 0.320 mmol), 2-bromoacetophenone **55** (75.0 mg, 0.380 mmol) and potassium carbonate (47.0 mg, 0.320 mmol) in acetone (1 mL) were used. The crude product was purified by flash column chromatography eluting with 0-60% ethyl acetate in 40-60 petroleum ether to yield the title compound **128** as a white solid (57.0 mg, 0.110 mmol, 33%).

R_f = 0.47 (40% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +43.5 (c = 0.2 in CH_3OH)

IR: ν_{max} = 3318 (w, N-H), 3290 (w, br, O-H), 2988 (s, C-H), 2901 (s, C-H), 1689 (s, C=O), 1598 (w, C=C), 1515 (m, C=C), 1474 (m, C=C), 1448 (m, C=C)

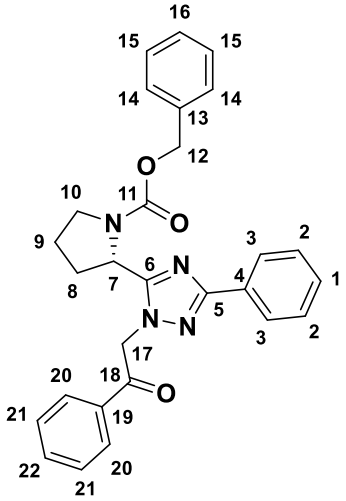
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 9.18 (1H, s, H13), 8.04 (2H, d, *J* = 7.8 Hz, H24), 7.95 - 8.05 (3H,m , H3 & 14), 7.72 (1H, t, *J* = 7.8 Hz, H26), 7.59 (2H, t, *J* = 7.8 Hz, H25), 7.47 (2H, t, *J* = 7.6 Hz, H2), 7.39 - 7.44 (1H, m, H1), 7.23 - 7.28 (3H, m, H19 & 20), 7.08 (3H, t, *J* = 8.5 Hz, H10 & 18), 6.62 (2H, d, *J* = 8.5 Hz, H11), 6.13 (1H, d, *J* = 18.6 Hz, H21a), 5.97 (1H, d, *J* = 18.6 Hz, H21b), 4.90 (1H,

td, *J* = 10.0, 5.3 Hz, H7), 4.79 (1H, d, *J* = 13.0 Hz, H16a), 4.69 (1H, d, *J* = 13.0 Hz, H16b), 3.15 (1H, dd, *J* = 14.0, 10.0 Hz, H8a), 3.09 (1H, dd, *J* = 14.0, 5.3 Hz, H8b)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 192.8 (C22), 160.2 (C5), 158.7 (C6), 156.3, 156.3 (C12 & 15), 137.2 (C17), 124.8 (C23), 134.7 (C26), 134.5 (C4), 131.2 (C9), 130.7 (C10), 129.4 (C1), 129.3 (C25), 128.7 (C2), 128.6 (C24), 128.2, 128.1 (C19 & 20), 127.6 (C18), 126.1 (C3), 115.4 (C11), 65.7 (C16), 55.4 (C21), 48.5 (C7), 37.8 (C8)

HRMS (ESI+): found $[M + H]^+$ 533.2178, $C_{32}H_{29}N_4O_4^+$ required 533.2162.

5.2.5.12. Benzyl (S)-2-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)pyrrolidine-1-carboxylate (129)



Following General Procedure 5: benzyl (*S*)-2-(3-phenyl-1*H*-1,2,4-triazol-5-yl)pyrrolidine-1-carboxylate **111** (300 mg, 0.860 mmol), 2-bromoacetophenone **55** (180 mg, 0.900 mmol) and potassium carbonate (119 mg, 0.860 mmol) in DMF (2 mL) were used. The crude product was purified by flash column chromatography eluting with 0-50% ethyl acetate in 40-60 petroleum ether to yield the title compound **129** as a pale yellow solid (322 mg, 0.690 mmol, 80%).

R_f = 0.41 (30% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +3.9 (c = 0.4 in $CHCl_3$)

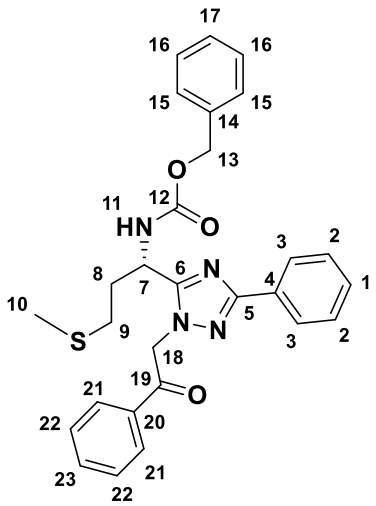
IR: ν_{max} = 2987 (s, C-H), 2901 (s, C-H), 1694 (s, C=O), 1597 (w, C=C), 1581 (w, C=C), 1479 (w, C=C), 1446 (m, C=C), 1410 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.12 (2H, d, *J* = 7.3 Hz, H20), 7.94 - 8.01 (5H, m, H3 & 20), 7.71 - 7.79 (2H, m, H22), 7.57 - 7.66 (4H, m, H21), 7.39 - 7.51 (6H, m, H1 & 2), 7.26 - 7.36 (5H, m, H15 & 16), 7.15 - 7.25 (2H, m, H14), 7.09 (2H, d, *J* = 7.3 Hz, H14), 6.24 (1H, d, *J* = 18.6 Hz, H17a), 6.13 (1H, d, *J* = 18.6 Hz, H17b), 5.90 (1H, d, *J* = 18.6 Hz, H17a), 5.79 (1H, d, *J* = 18.6 Hz, H17b), 5.11 (1H, dd, *J* = 7.2, 4.1 Hz, H7), 5.06 (1H, dd, *J* = 7.2, 4.1 Hz, H7), 5.00 - 5.05 (2H, m, H12), 4.93 - 5.00 (2H, m, H12), 3.56 - 3.65 (2H, m, H10a), 3.48 - 3.55 (2H, m, H10b), 2.28 - 2.42 (2H, m, H9a), 2.16 - 2.28 (2H, m, H8a), 2.08 - 2.01 (2H, m, H8b), 1.85 - 2.00 (2H, m, H9b) – mixture of rotamers.

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 193.1, 192.8 (C18), 160.4, 160.2 (C5), 159.6, 159.1 (C6), 154.6, 153.8 (C11), 137.3, 137.2 (C13), 134.7, 134.6, 134.5 (C19 & 22), 131.3 (C4), 129.6 (C1), 129.4, 129.4 (C21), 129.2 (C2), 128.8, 128.7 (C20), 128.6 (C15), 128.2, 128.1 (C16), 127.8, 127.8 (C14), 126.2, 126.1 (C3), 66.5 (C12), 55.4, 55.0 (C17), 52.3, 51.7 (C7), 47.4, 46.8 (C10), 33.0, 31.8 (C8), 24.6, 23.6 (C9)

HRMS (ESI+): found $[M + H]^+$ 467.2071, $C_{28}H_{27}N_4O_3^+$ required 467.2083.

5.2.5.13. Benzyl (S)-(3-(methylthio)-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)propyl)carbamate (130)



Following General Procedure 5: benzyl (*S*)-(3-(methylthio)-1-(3-phenyl-1*H*-1,2,4-triazol-5-yl)propyl)carbamate **112** (500 mg, 1.00 mmol), 2-bromoacetophenone **55** (239 mg, 1.20 mmol) and potassium carbonate (138 mg, 1.00 mmol) in DMF (2 mL)were used. The crude product was purified by flash column chromatography eluting with -60% ethyl acetate in 40-60 petroleum ether to yield the title compound **130** as a white solid (468 mg, 0.930 mmol, 93%).

R_f = 0.90 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -23.1 (c = 0.2 in $CHCl_3$)

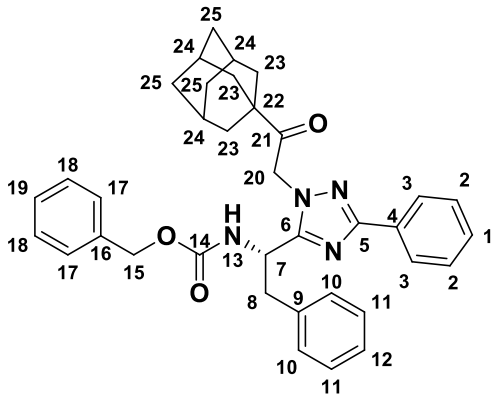
IR: ν_{max} = 3280 (w, N-H), 2987 (s, C-H), 2901 (s, C-H), 1691 (s, C=O), 1596 (w, C=C), 1526 (m, C=C), 1512 (m, C=C), 1475 (m, C=C), 1445 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.08 (1H, d, *J* = 8.2 Hz, H11), 8.05 (2H, d, *J* = 7.8 Hz, H21), 7.97 (2H, dd, *J* = 8.4, 1.4 Hz, H3), 7.69 - 7.78 (1H, m, H23), 7.60 (2H, t, *J* = 7.8 Hz, H22), 7.44 - 7.48 (2H, m, H2), 7.41 (1H, m, *J* = 1.4 Hz, H1), 7.29 - 7.32 (5H, m, H15, 16 & 17), 6.17 (1H, d, *J* = 18.5 Hz, H18a), 6.04 (1H, d, *J* = 18.5 Hz, H18b), 4.92 (1H, d, *J* = 12.5 Hz, H13a), 4.85 - 4.90 (1H, m, H7), 4.83 (1H, d, *J* = 12.5 Hz, H13b), 2.42 - 2.52 (1H, m, H9a), 2.41 - 2.47 (1H, m, H9b), 2.17 (2H, m, H8), 1.99 (3H, s, H10)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 192.9 (C19), 160.3 (C5), 158.6 (C6), 156.5 (C12), 137.1 (C14), 134.7, 134.6 (C20 & 23), 131.3 (C4), 129.6 (C1), 129.4, 129.2 (C2 & 22), 128.8, 128.7 (C16 & 21), 128.3 (C17), 128.1 (C15), 126.1 (C3), 66.1 (C13), 55.5 (C18), 45.7 (C7), 32.5 (C8), 30.0 (C9), 14.9 (C10)

HRMS (ESI+): found $[M + H]^+$ 501.1946, $C_{28}H_{29}N_4O_3S^+$ required 501.1960.

5.2.5.14. (S)-benzyl 1-(1-(2-oxo-2-((1R,3R)-adamantan-1-yl)ethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethylcarbamate (131)



Following General Procedure 5: benzyl (*S*)-(2-phenyl-1-(3-phenyl-1*H*-1,2,4-triazol-5-yl)ethyl)carbamate **54** (300 mg, 0.750 mmol), 1-((3*R*, 5*R*, 7*R*)-adamantam-1-yl)-2-bromo-ethan-1-one **113** (232 mg, 0.900 mmol) and potassium carbonate (104 mg, 0.750 mmol) in DMF (2 mL), was used.

The crude product was purified by flash column chromatography eluting with 0-40% ethyl acetate in 40-60 petroleum ether to yield the title compound **131** as a white solid (374 mg, 0.650 mmol, 87%).

R_f = 0.67 (30% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -20.7 (c = 0.4 in $CHCl_3$)

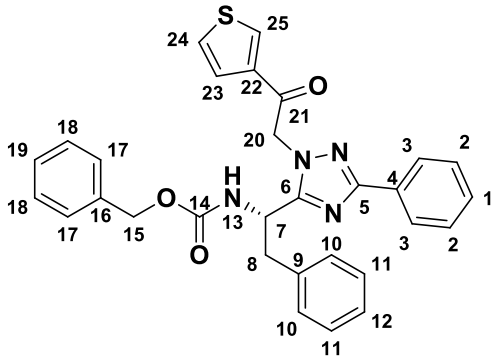
IR: ν_{max} = 3313 (w, N-H), 2971 (s, C-H), 2902 (w, C-H), 1698 (s, C=O), 1536 (m, C=C), 1475 (m, C=C), 1445 (m, C=C), 1404 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.12 (1H, d, *J* = 8.9 Hz, H13), 7.97 (2H, dt, *J* = 7.4, 1.4 Hz, H3), 7.46 (2H, t, *J* = 7.4 Hz, H2), 7.41 (1H, tt, *J* = 7.4, 1.4 Hz, H1), 7.24 - 7.31 (7H, m, H10, 11, 18 & 19), 7.21 (1H, tt, *J* = 6.6, 2.5 Hz, H12), 7.16 (2H, d, *J* = 6.1 Hz, H17), 5.53 (1H, d, *J* = 18.5 Hz, H20a), 5.46 (1H, d, *J* = 18.5 Hz, H20b), 4.93 (1H, d, *J* = 12.5 Hz, H15a), 4.87 (1H, d, *J* = 12.5 Hz, H15b), 4.78 (1H, ddd, *J* = 10.1, 8.9, 4.6 Hz, H7), 3.26 (1H, dd, *J* = 13.7, 10.1 Hz, H8a), 3.15 (1H, dd, *J* = 13.7, 4.6 Hz, H8b), 2.01 (3H, br s, H24), 1.87 (6H, q, *J* = 12.2 Hz, H23), 1.69 (6H, br s, H25)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 207.7 (C21), 160.1 (C5), 158.4 (C6), 156.4 (C14), 138.2 (C9), 137.2 (C16), 131.3 (C4), 129.8 (C11), 129.6 (C1), 129.2 (C2), 128.7, 128.6, 128.2 (C10, 18 & 19), 127.8 (C17), 126.9 (C12), 126.1 (C3), 65.9 (C15), 53.9 (C20), 48.2 (C7), 45.4 (C22), 38.6 (C8), 37.6 (C23), 36.3 (C25), 27.7 (C24)

HRMS (ESI+): found $[M + H]^+$ 575.3016, $C_{36}H_{39}N_4O_3^+$ required 575.3022.

5.2.5.15. (S)-benzyl 1-(1-(2-oxo-2-(thiophen-3-yl)ethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethylcarbamate (132)



Following General Procedure 5: benzyl (*S*)-(2-phenyl-1-(3-phenyl-1*H*-1,2,4-triazol-5-yl)ethyl)carbamate **54** (400 mg, 1.00 mmol), 2-bromo-1-(thiophen-3-yl)ethan-1-one **114** (199 mg 1.20

mmol) and potassium carbonate (138 mg, 1.00 mmol) in DMF (4 mL) were used. The crude product was purified by flash column chromatography eluting with 0-60% ethyl acetate in 40-60 petroleum ether to yield the title compound **132** as a white solid (321 mg, 0.610 mmol, 61%).

R_f = 0.52 (50% EtOAc in heptane)

$[\alpha]_D^{20}$ = +7.1 (c = 0.4 in $CHCl_3$)

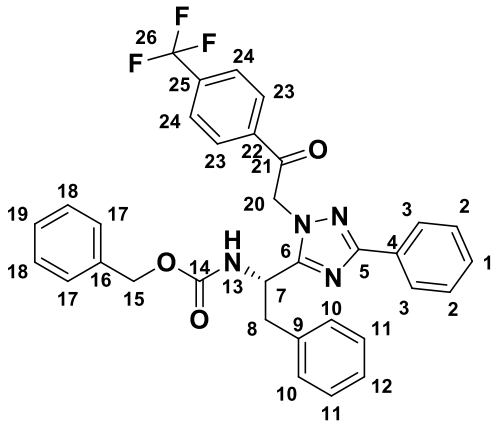
IR: ν_{max} = 3298 (w, N-H), 2988 (s, C-H), 2901 (s, C-H), 1693 (s, C=O), 1532 (m, C=C), 1475 (m, C=C), 1445 (m, C=C), 1404 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.70 (1H, dd, *J* = 2.7, 1.2 Hz, H25), 8.12 (1H, d, *J* = 8.5 Hz, H13), 7.95 - 8.03 (2H, m, H3), 7.72 (1H, dd, *J* = 5.2, 2.7 Hz, H24), 7.57 (1H, dd, *J* = 5.2, 1.2 Hz, H23), 7.47 (2H, t, *J* = 7.2 Hz, H2), 7.42 (1H, t, *J* = 7.2 Hz, H1), 7.29 7.32 (2H, m, H11), 7.22 - 7.29 (5H, m, H10, 18 & 19), 7.19 (1H, t, *J* = 7.3 Hz, H12), 7.12 (2H, dd, *J* = 7.5, 1.7 Hz, H17), 6.03 (1H, d, *J* = 18.3 Hz, H20a), 5.87 (1H, d, *J* = 18.3 Hz, H20b), 4.98 (1H, ddd, *J* = 10.1, 8.5, 4.9 Hz, H7), 4.83 (1H, d, *J* = 12.5 Hz, H15a), 4.74 (1H, d, *J* = 12.5 Hz, H15b), 3.27 (1H, dd, *J* = 14.5, 10.1 Hz, H8a), 3.21 (1H, dd, *J* = 14.5, 4.9 Hz, H8b)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 187.2 (C21), 160.2 (C5), 158.7 (C6), 156.3 (C14), 139.2 (C22), 138.2 (C9), 137.2 (C16), 135.4 (C25), 131.3 (C4), 129.8 (C11), 129.6 (C1), 129.2 (C2), 128.7, 128.6 (C10 & 18), 128.5 (C19), 128.1 (C24), 127.8 (C17), 126.9, 126.9 (C12 & 23), 126.1 (C3), 65.8 (C15), 55.7 (C20), 48.3 (C7), 38.6 (C8)

HRMS (ESI+): found $[M + H]^+$ 545.1615, $C_{30}H_{26}N_4O_3SNa^+$ required 5454.1618.

5.2.5.16. (S)-benzyl 1-(1-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethylcarbamate (133)



Following General Procedure 5: benzyl (*S*)-(2-phenyl-1-(3-phenyl-1*H*-1,2,4-triazol-5-yl)ethyl)carbamate **54** (300 mg, 0.750 mmol), 2-bromo-1-(4-(trifluoromethyl)phenyl)ethan-1-one **115** (240 mg, 0.900 mmol) and potassium carbonate (104 mg, 0.750 mmol) in acetone (1.5 mL) were used. The crude product was purified by flash column chromatography eluting with 0-40% ethyl acetate in 40-60 petroleum ether to yield the title compound **133** as a white solid (290 mg, 0.500 mmol, 66%).

R_f = 0.67 (50% EtOAc in heptane)

$[\alpha]_D^{20}$ = +3.8 (c = 0.4 in $CHCl_3$)

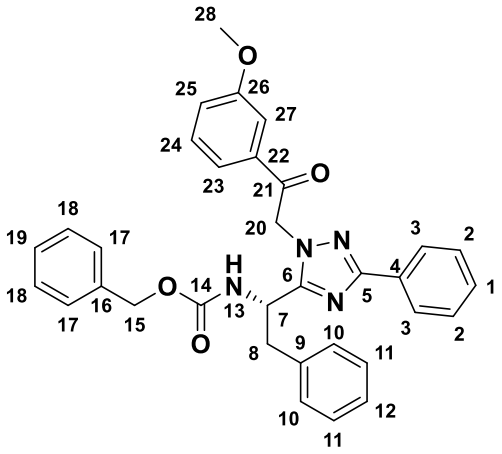
IR: ν_{max} = 3310 (w, N-H), 2974 (s, C-H), 2901 (s, C-H), 1698 (s, C=O), 1535 (m, C=C), 1475 (m, C=C), 1445 (m, C=C), 1408 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.21 (2H, d, *J* = 8.2 Hz, H23), 8.09 (1H, d, *J* = 9.4 Hz, H13), 7.99 - 8.03 (2H, m, H3), 7.96 (2H, d, *J* = 8.2 Hz, H24), 7.45 - 7.51 (2H, m, H2), 7.42 (1H, tt, *J* = 7.3, 1.8 Hz, H1), 7.31 (2H, d, *J* = 7.0 Hz, H11), 7.16 - 7.28 (6H, m, H10, 12, 18 & 19), 7.06 (2H, dd, *J* = 7.2, 2.3 Hz, H17), 6.23 (1H, d, *J* = 18.6 Hz, H20a), 6.06 (1H, d, *J* = 18.6 Hz, H20b), 5.06 (1H, td, *J* = 9.4, 5.0 Hz, H7), 4.76 (1H, d, *J* = 12.5 Hz, H15a), 4.67 (1H, d, *J* = 12.5 Hz, H15b), 3.26 - 3.30 (1H, m, H8a), 3.22 (1H, dd, *J* = 14.0, 5.0 Hz, H8b)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 192.5 (C21), 160.3 (C5), 158.6 (C6), 156.2 (C14), 138.1, 137.8 (C9 & 22), 137.2 (C16), 133.7 (C25), 131.3 (C4), 129.9 (C11), 129.6 (C1), 129.3 (C23), 129.1 (C10), 128.7, 128.5 (C2 & 18), 128.1 (C19), 127.7 (C17), 126.9 (C12), 126.3, 126.2 (C3 & 24), 123.1 (C26), 65.7 (C15), 55.8 (C20), 48.0 (C7), 38.5 (C8)

HRMS (ESI+): found $[M + H]^+$ 585.2093, $C_{33}H_{28}F_3N_4O_3^+$ required 585.2114.

5.2.5.17. Benzyl (S)-(1-(1-(2-(3-methoxyphenyl)-2-oxoethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (134)



Following General Procedure 5: benzyl (*S*)-(2-phenyl-1-(3-phenyl-1*H*-1,2,4-triazol-5-yl)ethyl)carbamate **54** (200 mg, 0.500 mmol), 2-bromo-3'-methoxyacetophenone **116** (137 mg, 0.600 mmol) and potassium carbonate (69.0 mg, 0.500 mmol) in acetone (1 mL). The crude product was purified by flash column chromatography eluting with 0-60% ethyl acetate in 40-60 petroleum ether to yield the title compound **134** as a white solid (137 mg, 0.250 mmol, 50%).

R_f = 0.74 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +10.0 (c = 0.3 in $CHCl_3$)

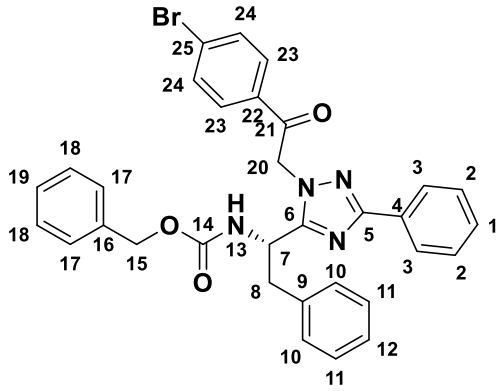
IR: ν_{max} = 3300 (w, N-H), 2972 (s, C-H), 2901 (s, C-H), 1698 (s, C=O), 1536 (m, C=C), 1475 (m, C=C), 1445 (m, C=C), 1408 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.11 (2H, d, *J* = 7.0 Hz, H3), 7.40 - 7.52 (7H, m, H1, 2, 18, 24 & 25), 7.29 - 7.36 (5H, m, H10, 12, 19 & 27), 7.23 - 7.27 (2H, m, H17), 7.22 (1H, dd, *J* = 2.6, 1.1 Hz, H23), 7.21 (2H, dt, *J* = 4.0, 1.5 Hz, H11), 5.58 - 5.70 (2H, m, H13 & 20a), 5.32 (1H, d, *J* = 18.0 Hz, H20b), 5.03 (1H, d, *J* = 12.2 Hz, H15a), 4.92 - 4.99 (2H, m, H7 & 15b), 3.88 (3H, s, H28), 3.43 (1H, dd, *J*=14.0, 7.9 Hz, H8a), 3.39 (1H, dd, *J* = 14.0, 6.4 Hz, H8b)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 191.0 (C21), 161.4 (C5), 160.0 (C26), 157.3 (C6), 155.9 (C14), 136.6 (C22), 136.0 (C9), 135.4 (C16), 130.8 (C4), 130.0 (C18), 129.4 (C11), 129.2 (C1), 128.7 (C10), 128.5, 128.5 (C2 & 27), 128.1 (C19), 127.8 (C17), 127.0 (C12), 126.4 (C3), 120.9, 120.6 (C23 & 24), 112.3 (C25), 67.0 (C15), 55.5 (C28), 54.5 (C20), 48.7 (C7), 40.6 (C8)

HRMS (ESI+): found $[M + H]^+$ 547.2343, $C_{33}H_{31}N_4O_4^+$ required 547.2345.

5.2.5.18. Benzyl (S)-(1-(1-(2-(4-bromophenyl)-2-oxoethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (135)



Following General Procedure 5: benzyl (*S*)-(2-phenyl-1-(3-phenyl-1*H*-1,2,4-triazol-5-yl)ethyl)carbamate **54** (400 mg, 1.00 mmol), 2,4'-dibromoacetophenone **117** (335 mg, 1.21 mmol) and potassium carbonate (139 mg, 1.00 mmol) in DMF (5 mL) were used. The crude product was purified by flash column chromatography eluting with 0-40% ethyl acetate in 40-60 petroleum ether to yield the title compound **135** as a white solid (486 mg, 0.820 mmol, 82%).

R_f = 0.62 (30% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +17.1 (c = 0.4 in $CHCl_3$)

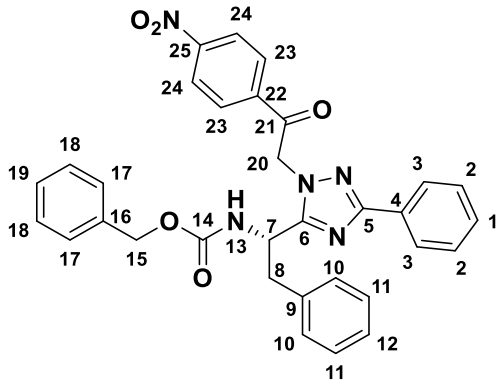
IR: ν_{max} = 3307 (w, N-H), 2973 (s, C-H), 2901 (s, C-H), 1698 (s, C=O), 1536 (m, C=C), 1475 (w, C=C), 1445 (m, C=C), 1407 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.10 (1H, d, *J* = 9.4 Hz, H13), 8.01 (2H, dd, *J* = 7.6, 1.2 Hz, H3), 7.97 (2H, d, *J* = 8.5 Hz, H23), 7.81 (2H, d, *J* = 8.5 Hz, H24), 7.48 (2H, t, *J* = 7.6 Hz, H2), 7.43 (1H, tt, *J* = 7.6, 1.2 Hz, H1), 7.28 - 7.33 (2H, m, H11), 7.30 – 7.22 (5H, m, H10, 18 & 19), 7.20 (1H, t, *J* = 7.0 Hz, H12), 7.09 (2H, dd, *J* = 7.2, 2.0 Hz, H17), 6.16 (1H, d, *J* = 18.6 Hz, H20a), 5.98 (1H, d, *J* = 18.6 Hz, H20b), 5.04 (1H, td, *J* = 9.4, 5.0 Hz, H7), 4.79 (1H, d, *J* = 12.5 Hz, H15a), 4.69 (1H, d, *J* = 12.5 Hz, H15b), 3.29 (1H, dd, *J* = 14.0, 9.4 Hz, H8a), 3.23 (1H, dd, *J* = 14.0, 5.0 Hz, H8b)

^{13}C NMR (126 MHz, d_6-DMSO): δ_c = 192.2 (C21), 160.2 (C5), 158.6 (C6), 156.3 (C14), 138.1 (C9), 137.2 (C16), 133.6 (C22), 132.5 (C24), 131.3 (C4), 130.6 (C23), 129.8 (C11), 129.6 (C1), 129.2 (C2), 128.8, 128.7, 128.5 (C10, 18 & 25), 128.1 (C19), 127.7 (C17), 126.9 (C12), 126.1 (C3), 65.7 (C15), 55.5 (C20), 48.1 (C7), 38.6 (C8)

HRMS (ESI+): found $[M + H]^+$ 595.1358, $C_{32}H_{28}BrN_4O_3^+$ required 595.1345.

5.2.5.19. Benzyl (S)-(1-(1-(2-(4-nitrophenyl)-2-oxoethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (136)



Following General Procedure 5: benzyl (*S*)-(2-phenyl-1-(3-phenyl-1*H*-1,2,4-triazol-5-yl)ethyl)carbamate **54** (185 mg, 0.460 mmol), 2-bromo-4'-nitroacetophenone **118** (136 mg, 0.560 mmol) and potassium carbonate (64.0 mg, 0.460 mmol) in DMF (5 mL) were used. The crude product was purified by flash column chromatography eluting with 0-40% ethyl acetate in 40-60 petroleum ether to yield the title compound **136** as a yellow solid (131 mg, 0.230 mmol, 50%).

R_f = 0.24 (30% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +18.3 (c = 0.1 in $CHCl_3$)

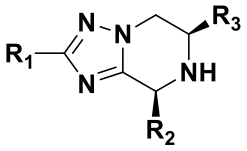
IR: ν_{max} = 3299 (w, N-H), 2971 (s, C-H), 2901 (s, C-H), 1698 (s, C=O), 1536 (s, N-O), 1475 (m, C=C), 1445 (m, C=C), 1407 (m, C=C), 1324 (m, N-O)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.38 (2H, d, *J* = 8.9 Hz, H24), 8.24 (2H, d, *J* = 8.9 Hz, H23), 8.10 (1H, d, *J* = 9.4 Hz, H13), 8.00 (2H, d, *J* = 7.3 Hz, H3), 7.48 (2H, t, *J* = 7.3 Hz, H2), 7.43 (1H, t, *J* = 7.3 Hz, H1), 7.31 (2H, d, *J* = 7.3 Hz, H11), 7.15 - 7.26 (6H, m, H10, 12, 18 & 19), 7.04 - 7.10 (2H, m, H17), 6.26 (1H, d, *J* = 18.6 Hz, H20a), 6.07 (1H, d, *J* = 18.6 Hz, H20b), 5.08 (1H, td, *J* = 9.4, 5.0 Hz, H7), 4.77 (1H, d, *J* = 12.5 Hz, H15a), 4.68 (1H, d, *J* = 12.5 Hz, H15b), 3.26 - 3.30 (1H, m, H8a), 3.23 (1H, dd, *J* = 14.0, 5.0 Hz, H8b)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 192.3 (C21), 160.3 (C5), 158.7 (C6), 156.3 (C14), 150.8 (C25), 139.3 (C22), 138.0 (C9), 137.2 (C16), 131.3 (C4), 130.1 (C23), 129.9 (C11), 129.7 (C1), 129.3 (C2), 128.7, 128.5 (C10 & 18), 128.1 (C19), 127.7 (C17), 126.9 (C12), 126.2 (C3), 124.4 (C24), 65.7 (C15), 55.9 (C20), 47.9 (C7), 38.5 (C8)

HRMS (ESI+): found $[M + H]^+$ 562.2106, $C_{32}H_{28}N_5O_5^+$ required 562.2090.

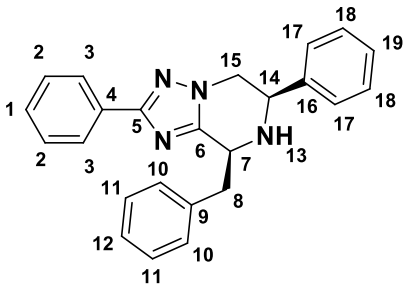
5.2.6. General procedure for Cyclisation to the Amine



General Procedure 6: To a stirred solution of benzyl –(*S*)-(2-R_2-((3-R_1-1*H*-1,2,4-triazol-5-yl)methyl)carbamate (1.0 eq.) in minimal ethyl acetate, methanol and water (v/v, 3:1), was added ammonium formate (30 eq.) and palladium dihydroxide (20 mol %). The mixture was stirred overnight until complete conversion to the amine was observed. The catalyst was removed by filtration through celite and the filter pad washed with methanol (3 x 30 mL). The solvent was removed under reduced pressure. The crude compound was purified by flash column chromatography on silica to yield the title compound.

For the purpose of stability, to a stirred solution of the title compound in minimal dichloromethane was added hydrochloride solution (10 eq., 2M in diethyl ether), and the desired salt collected by filtration.

5.2.6.1. (6R,8S)-8-benzyl-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (58)



Following General Procedure 6: benzyl (*S*)-(1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1*H*-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **56** (188 mg, 364 μmol), ammonium formate (688 mg, 10.9 mmol) and palladium dihydroxide (51.0 mg, 72.8 μmol) in ethyl acetate (1 mL), methanol and water (2 mL, 3:1 v:v,) were. The crude product was purified by flash column chromatography eluting with 0-40% ethyl acetate in 40-60 petroleum ether to yield the title compound **58** as a yellow solid (121 mg, 330 μmol, 91%).

$\mathbf{R}_f$ = 0.53 (30% EtOAc in 40-60 petroleum ether)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -94.3 (c = 0.3 in CH_3OH)

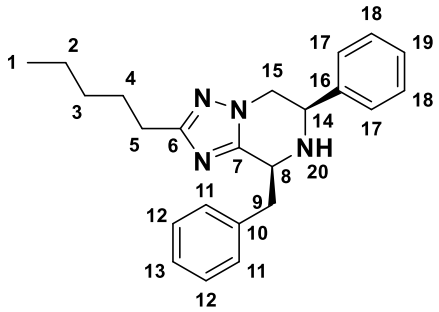
IR ν_{max} = 3028 (m, C-H), 1697 (m, C=N), 1602 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.07 - 8.14 (2H, m, H3), 7.65 - 7.70 (2H, m, H17), 7.55 - 7.60 (3H, m, H18 & 19), 7.54 (2H, d, *J* = 7.3 Hz, H10), 7.49 (3H, d, *J* = 6.4 Hz, H1 & 2), 7.42 (2H, t, *J* = 7.3 Hz, H11), 7.36 (1H, t, *J* = 7.3 Hz, H12), 5.31 (1H, dd, *J* = 8.9, 5.2 Hz, H7), 5.18 (1H, dd, *J* = 11.0, 5.8 Hz, H14), 4.84 (1H, dd, *J* = 14.0, 5.8 Hz, H15a), 4.81 (1H, dd, *J* = 14.0, 11.0 Hz, H15b), 3.96 (1H, dd, *J* = 14.8, 5.2 Hz, H8a), 3.42 (1H, dd, *J* = 14.8, 8.9 Hz, H8b)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 164.0 (C5), 151.2 (C6), 135.9 (C9), 133.4 (C16), 131.9 (C19), 131.7 (C4), 131.1 (C1), 131.0 (C10), 130.9 (C18), 130.3 (C11), 129.9 (C2), 129.4 (C17), 129.1 (C12), 127.6 (C3), 59.8 (C14), 58.2 (C7), 50.6 (C15), 38.1 (C8)

HRMS (ESI+): found $[M + H]^+$ 367.1931, $C_{24}H_{23}N_4^+$ required 367.1923.

5.2.6.2. (6R,8S)-8-benzyl-2-pentyl-6-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (137)



Following General Procedure 6: benzyl (*S*)-(1-(1-(2-oxo-2-phenylethyl)-3-(pent-4-en-1-yl)-1*H*-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **119** (102 mg, 201 μmol), ammonium formate (379 mg, 6.02 mmol) and palladium dihydroxide (28.0 mg, 40.1 μmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in hexane to yield the title compound **137** as a white solid (44.0 mg, 125 μmol, 60%).

$\mathbf{R_f}$ = 0.14 (20% EtOAc in hexane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -16.4 (c = 0.1 in CH_3OH)

IR ν_{max} = 2929 (m, C-H), 1508 (m, C=C)

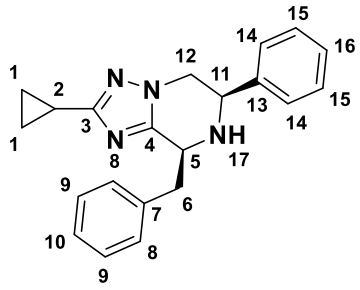
^{1}H NMR (500 MHz, CD_3OD): δ_H = 7.64 (2H, dd, *J* = 7.6, 4.0 Hz, H17), 7.51 - 7.55 (3H, m, H18 & 19), 7.47 (2H, d, *J* = 7.3 Hz, H11), 7.39 (2H, t, *J* = 7.3 Hz, H12), 7.32 (1H, t, *J* = 7.3 Hz, H13), 5.20 (1H, dd, *J* = 8.5, 3.7 Hz, H8), 5.04 (1H, dd, *J* = 7.9, 6.7 Hz, H16), 4.61 - 4.74 (2H, m, H15), 3.84 (1H,

dd, *J* = 14.8, 3.7 Hz, H9a), 3.37 (1H, dd, *J* = 14.8, 8.5 Hz, H9b), 2.78 (2H, t, *J* = 7.3 Hz, H5), 1.79 (2H, quin, *J* = 7.3 Hz, H4), 1.37 - 1.43 (4H, m, H2 & 3), 0.95 (3H, t, *J* = 6.7 Hz, H1)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 165.9 (C6), 150.7 (C7), 135.8 (C10), 133.9 (C16), 131.7 (C19), 130.9 (C11), 130.7 (C18), 130.3 (C12), 129.3 (C17), 129.1 (C13), 59.6 (C16), 57.8 (C8), 50.7 (C15), 38.0 (C9), 32.6 (C3), 29.0, 28.9 (C4 & 5), 23.6 (C2), 14.5 (C1)

HRMS (ESI+): found $[M + H]^+$ 361.2401, $C_{23}H_{29}N_4^+$ required 361.2392.

5.2.6.3. (6R,8S)-8-benzyl-2-cyclopropyl-6-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (138)



Following General Procedure 6: benzyl (*S*)-(1-(3-cyclopropyl-1-(2-oxo-2-phenylethyl)-1*H*-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **120** (100 mg, 208 μmol), ammonium formate (394 mg, 6.24 mmol) and palladium dihydroxide (29.0 mg, 41.6 μmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in hexane to yield the title compound **138** as a white solid (51.0 mg, 154 μmol, 74%).

R_f = 0.32 (30% EtOAc in hexane)

$[\alpha]_D^{20}$ = -40.5 (c = 0.2 in CH_3OH)

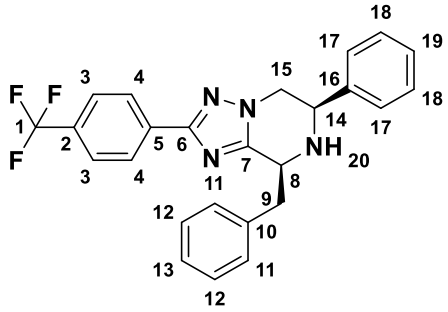
IR: ν_{max} = 2862 (m, C-H), 1575 (m,C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 7.60 (2H, dd, *J* = 3.7, 2.1 Hz, H14), 7.51 - 7.56 (3H, m, H15 & 16), 7.45 (2H, d, *J* = 7.0 Hz, H8), 7.39 (2H, ddt, *J* = 7.6, 7.0, 1.5 Hz, H9), 7.33 (1H, tt, *J* = 7.6, 1.5 Hz, H10), 5.17 (1H, dd, *J* = 8.9, 4.6 Hz, H5), 5.05 (1H, dd, *J* = 11.3, 5.2 Hz, H11), 4.64 - 4.70 (1H, m, H12a), 4.61 (1H, dd, *J* = 12.2, 5.2 Hz, H12b), 3.82 (1H, dd, *J* = 15.0, 4.6 Hz, H6a), 3.27 (1H, dd, *J* = 15.0, 8.9 Hz, H6b), 2.09 (1H, tt, *J* = 8.2, 5.0 Hz, H2), 1.03 - 1.07 (2H, m, H1a), 0.93 - 1.03 (2H, m, H1b)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 159.6 (C3), 150.4 (C4), 135.8 (C7), 133.6 (C13), 131.8 (C16), 130.9 (C8), 130.8 (C15), 130.3 (C9), 129.3 (C14), 129.1 (C10), 59.6 (C11), 57.9 (C5), 50.4 (C12), 38.1 (C6), 9.6 (C2), 8.7 (C1)

HRMS (ESI+): found $[M + H]^+$ 331.1923, $C_{21}H_{23}N_4^+$ required 331.1923.

5.2.6.4. (6R,8S)-8-benzyl-6-phenyl-2-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (139)



Following General Procedure 6: benzyl (*S*)-(1-(1-(2-oxo-2-phenylethyl)-3-(4-(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **121** (100 mg, 171 μmol), ammonium formate (323 mg, 5.13 mmol) and palladium dihydroxide (24.0 mg, 34.2 μmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in hexane to yield the title compound **139** as a white solid (44.0 mg, 101 μmol, 59%).

$\mathbf{R_f}$ = 0.82 (30% EtOAc in hexane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -98.2 (c = 0.3 in CH_3OH)

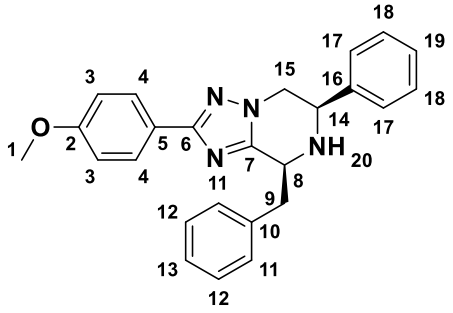
IR ν_{max} = 2972 (m, C-H), 1625 (m, C=N), 1529 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.27 (2H, d, *J* = 8.1 Hz, H4), 7.78 (2H, d, *J* = 8.1 Hz, H3), 7.67 - 7.71 (2H, m, H17), 7.50 - 7.57 (5H, m, H12, 18 & 19), 7.40 (2H, t, *J* = 7.3 Hz, H11), 7.33 (1H, tt, *J* = 7.3, 1.2 Hz, H13), 5.30 (1H, dd, *J* = 8.7, 5.3 Hz, H8), 5.16 (1H, dd, *J* = 9.8, 6.7 Hz, H15a), 4.80 - 4.85 (2H, m, H14 & 15b) 3.93 (1H, dd, *J* = 14.8, 5.33 Hz, H9a), 3.45 (1H, dd, *J* = 14.8, 8.7 Hz, H9b)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 162.7 (C6), 151.8 (C7), 136.0 (C10), 135.5 (C5), 133.5 (C16), 132.7 (C2), 131.9 (C19), 131.0 (C12), 130.9 (C18), 130.3 (C11), 129.5 (C17), 129.0 (C13), 128.0 (C4), 126.9 (C3), 124.6 (C1), 59.8 (C15), 58.1 (C8), 50.8 (C14), 38.0 (C9)

HRMS (ESI+): found $[M + H]^+$ 435.1790, $C_{25}H_{22}N_4F_3^+$ required 435.1797.

5.2.6.5. (6R,8S)-8-benzyl-2-(4-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (141)



Following General Procedure 6: benzyl (*S*)-(1-(3-(4-methoxyphenyl)-1-(2-oxo-2-phenylethyl)-1*H*-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **123** (137 mg, 251 μmol), ammonium formate (474 mg, 7.52 mmol) and palladium dihydroxide (35.0 mg, 50.1 μmol) in methanol and water (1 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in hexane to yield the title compound **141** as a white solid (78.1 mg, 197 μmol, 77%).

$\mathbf{R_f}$ = 0.39 (30% EtOAc in hexane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -48.6 (c = 0.3 in CH_3OH)

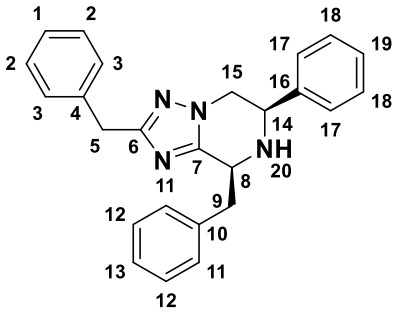
IR ν_{max} = 2969 (m, C-H), 1611 (m, C=N), 1539 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.01 (2H, dt, *J* = 9.1, 2.1 Hz, H4), 7.65 - 7.69 (2H, m, H17), 7.51 - 7.56 (4H, m, H10 & 18), 7.50 (1H, s, H19), 7.39 (2H, t, *J* = 7.5 Hz, H11), 7.32 (1H, t, *J* = 7.5 Hz, H12), 7.01 (2H, dt, *J* = 9.1, 2.7 Hz, H3), 5.26 (1H, dd, *J* = 8.7, 4.7 Hz, H8), 5.14 (1H, dd, *J* = 10.1, 6.4 Hz, H15), 4.74 - 4.81 (2H, m, H14), 3.93 (1H, dd, *J* = 14.8, 4.7 Hz, H9a), 3.85 (3H, s, H1), 3.42 (1H, dd, *J* = 14.8, 8.7 Hz, H9b)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 163.9 (C6), 162.8 (C2), 151.0 (C7), 136.0 (C10), 133.4 (C16), 131.9 (C18), 131.0 (C19), 130.8 (C12), 130.3 (C11), 129.5 (C17), 129.1, 129.1 (C4 & 13), 124.1 (C5), 115.3 (C3), 59.3 (C15), 58.2 (C8), 56.0 (C1), 50.5 (C14), 38.0 (C9)

HRMS (ESI+): found $[M + H]^+$ 397.2029, $C_{25}H_{24}N_4O^+$ required 397.2028.

5.2.6.6. (6R,8S)-8-benzyl-2-(4-bromobenzyl)-6-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (142)



Following General Procedure 6: benzyl (*S*)-(1-(3-(4-bromobenzyl)-1-(2-oxo-2-phenylethyl)-1*H*-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **124** (19.9 mg, 32.7 μmol), ammonium formate (62.1 mg, 98.1 μmol) and palladium dihydroxide (4.60 mg, 6.54 μmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with 50% ethyl acetate in hexane to yield the title compound **142** as a white solid (4.70 mg, 12.4 μmol, 38%).

$\mathbf{R_f}$ = 0.41 (60% EtOAc in hexane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -38.3 (c = 0.1 in CH_3OH)

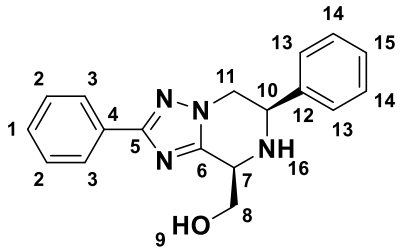
IR: ν_{max} = 2927 (m, C-H), 1603 (w, C=C), 1495 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 7.55 (2H, dd, *J* = 7.6, 1.5 Hz, H17), 7.45 – 7.49 (3H, m, H18 & 19), 7.38 (2H, d, *J* = 7.0 Hz, H2), 7.28 - 7.35 (7H, m, H1, 3, 11 & 12), 7.22 - 7.26 (1H, m, H13), 4.71 - 4.82 (1H, m, H14), 4.53 (1H, d, *J* = 11.3 Hz, H15a), 4.36 - 4.40 (1H, m H15b), 4.09 (2H, s, H5), 3.71 (1H, dd, *J* = 14.5, 3.2 Hz, H9a), 3.21 (1H, dd, *J* = 14.5, 8.9 Hz, H9b) – H8 obscured by MeOD peak

^{13}C NMR (126 MHz, CD_3OD): δ_C = 169.0 (C6), 167.8 (C7), 139.2 (C4), 135.4 (C9), 135.1 (C16), 130.9 (C2), 130.9 (C18), 130.5 (C19), 130.0 (C1), 130.0 (C11), 129.7 (C3), 128.9 (C17), 128.6 (C13), 127.8 (C12), 59.2 (C14), 59.1 (C8), 53.3 (C15), 37.0 (C9), 35.4 (C5)

HRMS (ESI+): found $[M + H]^+$ 381.2086, $C_{25}H_{25}N_4^+$ required 381.2079.

5.2.6.7. ((6R,8R)-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazin-8-yl)methanol (143)



Following General Procedure 6: benzyl (*S*)-(2-hydroxy-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1*H*-1,2,4-triazol-5-yl)ethyl)carbamate **143** (56.0 mg, 123 μmol), ammonium formate (232 mg, 3.68 mmol) and palladium dihydroxide (17.0 mg, 24.5 μmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with 80% ethyl acetate in hexane to yield the title compound **125** as a brown solid (31.0 mg, 101 μmol, 82%).

$\mathbf{R}_f$ = 0.44 (80% EtOAc in hexane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -108.6 (c = 0.3 in CH_3OH)

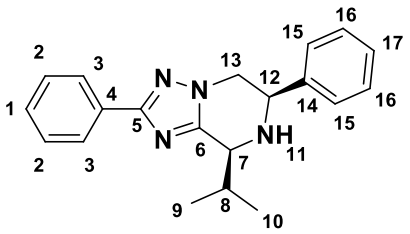
IR ν_{max} = 2927 (m, C-H), 1686 (m, C=N), 1611 (m, C=C), 1556 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.07 - 8.11 (2H, m, H3), 7.72 - 7.77 (2H, m, H13), 7.59 - 7.64 (3H, m, H14 & 15), 7.46 - 7.51 (3H, m, H1 & 2), 5.28 (1H, dd, *J* = 11.3, 4.9 Hz, H10), 5.14 (1H, dd, *J* = 7.3, 3.7 Hz, H7), 4.85 (1H, ddd, *J* = 13.7, 4.9, 0.6 Hz, H11a), 4.79 (1H, ddd, *J* = 13.7, 11.3, 1.2 Hz, H11b), 4.48 (1H, dd, *J* = 12.2, 3.7 Hz, H8a), 4.28 (1H, dd, *J* = 12.2, 7.3 Hz, H8b)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 164.1 (C5), 149.2 (C6), 133.3 (C4), 131.9 (C15), 131.6 (C12), 131.1 (C1), 130.9 (C14), 129.9 (C2), 129.4 (C13), 127.6 (C3), 60.6 (C8), 59.1 (C10), 58.6 (C7), 50.5 (C11)

HRMS (ESI+): found $[M + H]^+$ 307.1539, $C_{18}H_{19}N_4O$ required 307.1553.

5.2.6.8. (6R,8S)-8-isopropyl-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (144)



Following General Procedure 6: benzyl (*S*)-(2-methyl-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1*H*-1,2,4-triazol-5-yl)propyl)carbamate **126** (173 mg, 369 μmol), ammonium formate (693 mg, 11.1 mmol) and palladium dihydroxide (52.0 mg, 73.8 μmol) in ethyl acetate (1 mL), methanol and water (3 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in hexane to yield the title compound **144** as a white solid (99.0 mg, 311 μmol, 84%).

$\mathbf{R}_f$ = 0.66 (30% EtOAc in hexane)

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -64.8 (c = 0.2 in CH_3OH)

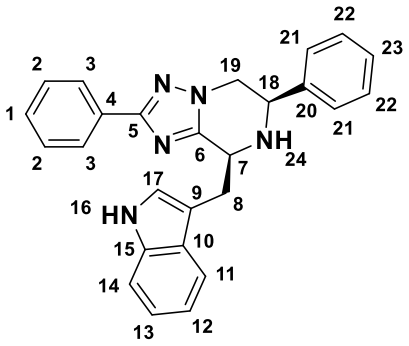
IR ν_{max} = 2974 (m, C-H), 2905 (m, C-H), 1537 (m, C=N), 1520 (m, C=C0, 1488 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.08 (2H, dd, *J* = 7.9, 1.8 Hz, H3), 7.74 - 7.79 (2H, m, H15), 7.56 - 7.61 (3H, m, H16 & 17), 7.43 - 7.48 (3H, m, H1 & 2), 5.22 (1H, dd, *J* = 11.4, 5.2 Hz, H12), 4.92 (1H, d, *J* = 4.9 Hz, H7), 4.82 (1H, dd, *J* = 13.7, 11.4 Hz, H13a), 4.78 (1H, dd, *J* = 13.7, 5.2 Hz, H13b), 2.65 (1H, dsep, *J* = 4.9, 7.0 Hz, H8), 1.38 (3H, d, *J* = 7.0 Hz, H9/10), 1.38 (3H, d, *J* = 7.0 Hz, H9/10)

^{13}C NMR (400 MHz, CD_3OD): δ_C = 163.9 (C5), 150.7 (C6), 133.3 (C14), 132.0 (C17), 131.8 (C4), 131.0 (C1), 130.9 (C16), 129.9 (C2), 129.7 (C15), 127.5 (C3), 62.5 (C7), 60.2 (C12), 50.4 (C13), 31.9 (C8), 19.7 (C9/10), 18.9 (C9/10)

HRMS (ESI+): found $[M + H]^+$ 319.1912, $C_{20}H_{23}N_4^+$ required 319.1923.

5.2.6.9. (6R,8S)-8-((1H-indol-3-yl)methyl)-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (145)



Following General Procedure 6: benzyl (*S*)-(2-(1H-indol-3-yl)-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1*H*-1,2,4-triazol-5-yl)ethyl)carbamate **125** (100 mg, 180 μmol), ammonium formate (340 mg, 5.40 mmol) and palladium dihydroxide (25.0 mg, 36.0 μmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v) were used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in hexane to yield the title compound **145** as an orange solid (68.0 mg, 168 μmol, 93%).

R_f = 0.41 (30% EtOAc in hexane)

$[\alpha]_D^{20}$ = -57.9 (c = 0.2 in CH_3OH)

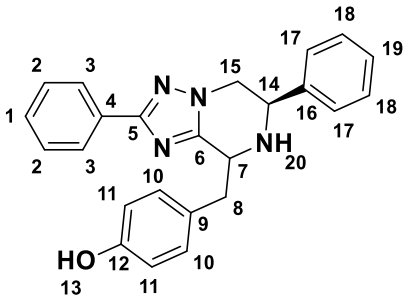
IR: ν_{max} = 2969 (m, C-H), 2920 (m, C-H), 1697 (m, C=N), 1618 (m, C=C), 1521 (m, C=C)

^{1}H NMR (400 MHz, CD_3OD): δ_H = 8.15 (2H, d, *J* = 7.8 Hz, H3), 7.80 (1H, d, *J* = 7.8 Hz, H11), 7.65 (2H, d, *J* = 3.7 Hz, H21), 7.47 - 7.57 (6H, m, H1, 2, 22 & 23), 7.41 (1H, d, *J* = 8.2 Hz, H14), 7.39 (1H, s, H17), 7.14 - 7.20 (1H, m, H13), 7.08 - 7.14 (1H, m, H12), 5.32 (1H, dd, *J* = 8.9, 3.1 Hz, H7), 5.14 (1H, dd, *J* = 9.4, 5.6 Hz, H18), 4.76 - 4.85 (2H, m, H19), 4.16 (1H, dd, *J* = 15.3, 3.1 Hz, H8a), 3.68 (1H, dd, *J* = 15.3, 8.9 Hz, H8b)

^{13}C NMR (101 MHz, CD_3OD): δ_H = 163.7 (C5), 151.3 (C6), 138.4 (C15), 133.3 (C20), 131.6 (C2), 131.4 (C4), 131.1 (C1), 130.7 (C22), 129.9 (C23), 129.7 (C21), 128.6 (C10), 127.6 (C3), 126.5 (C17), 123.0 (C13), 120.4 (C12), 119.3 (C11), 112.8 (C14), 107.9 (C9), 59.8 (C18), 57.6 (C7), 50.8 (C19), 28.1 (C8)

HRMS (ESI+): found $[M + H]^+$ 406.2027, $C_{26}H_{24}N_5^+$ required 406.2032.

5.2.6.10. 4-(((6R,8S)-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazin-8-yl)methyl)phenol (146)



Following General Procedure 6: benzyl (*S*)-(1-(1-(2-(4-hydroxyphenyl)-2-oxoethyl)-3-phenyl-1*H*-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **128** (54.0 mg, 101 μmol), ammonium formate (192 mg, 3.04 mmol) and palladium dihydroxide (14.0 mg, 20.3 μmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v) were used. The crude product was purified by flash column chromatography eluting with 50% ethyl acetate in hexane to yield the title compound **146** as a white solid (32.0 mg, 83.7 μmol, 83%).

R_f = 0.55 (55% EtOAc in hexane)

$[\alpha]_D^{20}$ = -87.6 (c = 0.2 in CH_3OH)

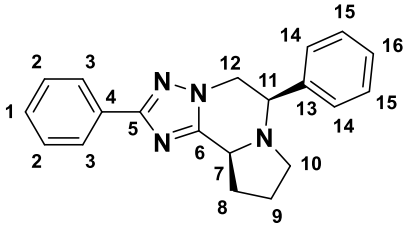
IR: ν_{max} = 3209 (m, br, O-H), 2929 (m, C-H), 1701 (m, C=N), 1612 (m, C=C), 1514 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.10 (2H, dd, *J* = 7.3, 1.5 Hz, H3), 7.68 (2H, d, *J* = 3.4 Hz, H17), 7.55 (3H, d, *J* = 3.4 Hz, H18 & 19), 7.43 - 7.52 (3H, m, H1 & 2), 7.33 (2H, d, *J* = 8.2 Hz, H10), 6.82 (2H, d, *J* = 8.2 Hz, H11), 5.09 - 5.25 (2H, m, H7 & 14), 4.80 (2H, d, *J* = 6.1 Hz, H15), 3.87 (1H, d, *J* = 13.7 Hz, H8a), 3.36 (1H, dd, *J* = 13.7, 8.2 Hz, H8b)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 164.0 (C5), 158.5 (C12), 151.3 (C6), 133.4 (C16), 132.1 (C11), 131.8 (C19), 131.7 (C18), 131.1 (C1), 130.8 (C4), 129.9 (C2), 129.5 (C17), 127.6 (C3), 126.2 (C9), 117.0 (C10), 59.8 (C14), 58.5 (C7), 50.6 (C15), 37.3 (C8)

HRMS (ESI+): found $[M + H]^+$ 383.1874, $C_{24}H_{22}N_4O^+$ required 383.1872.

5.2.6.11. (6R,10aS)-2,6-diphenyl-5,6,8,9,10,10a-hexahydropyrrolo[1,2-a][1,2,4]triazolo[5,1-c]pyrazine (147)



Following General Procedure 6: benzyl (*S*)-2-(1-(2-oxo-2-phenylethyl)-3-phenyl-1*H*-1,2,4-triazol-5-yl)pyrrolidine-1-carboxylate **129** (65.6 mg, 141 μmol), ammonium formate (267 mg, 4.24 mmol) and palladium dihydroxide (19.8 mg, 28.2 μmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v) were used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in hexane to yield the title compound **147** as a yellow solid (26.8 mg, 84.7 μmol, 60%).

R_f = 0.27 (30% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -29.3 (c = 0.1 in CH_3OH)

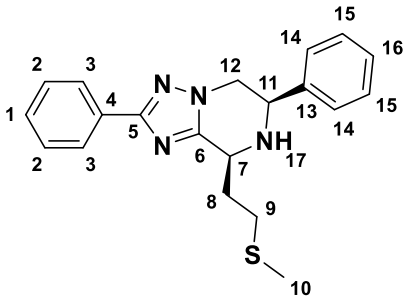
IR: ν_{max} = 2918 (m, C-H), 1703 (m, C=N), 1675 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.01 - 8.10 (2H, m, H3), 7.75 (2H, dd, *J* = 3.4, 2.1 Hz, H14), 7.57 - 7.63 (3H, m, H15 & 16), 7.43 - 7.50 (3H, m, H1 & 2), 5.57 (1H, dd, *J* = 11.7, 3.8 Hz, H11), 5.44 - 5.46 (1H, m, H7), 5.18 (1H, dd, *J* = 13.1, 11.7 Hz, H12a), 3.56 - 3.67 (1H, m, H8a), 2.72 (2H, t, *J* = 6.7 Hz, H10), 2.19 (1H, td, *J* = 14.3, 6.7 Hz, H9a), 2.10 (1H, td, *J* = 14.3, 6.7 Hz, H9b) – H8b & H12b obscured by solvent

^{13}C NMR (126 MHz, CD_3OD): δ_C = 164.2 (C5), 150.1 (C6), 132.5 (C16), 131.6 (C13), 131.4 (C4), 131.2 (C1), 131.1 (C15), 130.5 (C14), 130.0 (C2), 127.6 (C3), 62.9 (C7), 60.7 (C11), 52.5 (C8), 37.5 (C10), 22.7 (C9) –C12 obscured by solvent

HRMS (ESI+): found $[M + H]^+$ 317.1780, $C_{20}H_{21}N_4^+$ required 317.1766.

5.2.6.12. (6R,8S)-8-(2-(methylthio)ethyl)-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (148)



Following General Procedure 6: benzyl (*S*)-(3-(methylthio)-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1*H*-1,2,4-triazol-5-yl)propyl)carbamate **130** (123 mg, 245 μmol), ammonium formate (463 mg, 7.34mmol) and palladium dihydroxide (68.7 mg, 489 μmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v) were used. The crude product was purified by flash column chromatography eluting with 50% ethyl acetate in hexane to yield the title compound **148** as a white solid (43.7 mg, 125 μmol, 51%).

R_f = 0.50 (30% EtOAc in hexane)

$[\alpha]_D^{20}$ = -31.0 (c = 0.2 in CH_3OH)

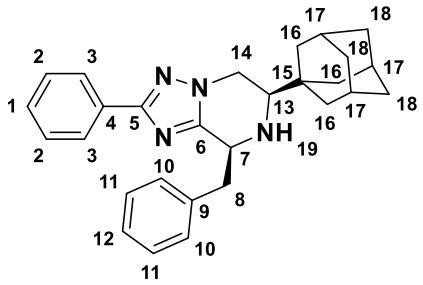
IR: ν_{max} = 2916 (m, C-H), 1705 (m, C=N), 1687 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.08 (2H, dd, *J* = 7.5, 2.1 Hz, H3), 7.66 - 7.71 (2H, m, H14), 7.57 - 7.62 (3H, m, H15 & 16), 7.42 - 7.48 (3H, m, H1 & 2), 5.25 (1H, dd, *J* = 11.7, 4.9 Hz, H11), 5.20 (1H, t, *J* = 6.6 Hz, H7), 4.82 (1H, dd, *J* = 13.7, 4.9 Hz, H12a), 4.73 (1H, dd, *J* = 13.7, 11.7 Hz, H12b), 3.05 - 3.17 (2H, m, H9), 2.70 (1H, td, *J* = 14.1, 7.4 Hz, H8a), 2.34 (1H, td, *J* = 14.1, 7.3 Hz, H8b), 2.21 (3H, s, H10)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 164.1 (C5), 151.4 (C6), 133.4 (C13), 132.1 (C16), 131.7 (C4), 131.1, 131.0 (C1 & 15), 129.9 (C2), 129.3 (C14), 127.5 (C3), 59.5 (C11), 55.2 (C7), 50.5 (C12), 31.7 (C8), 31.0 (C9), 15.2 (C10)

HRMS (ESI+): found $[M + H]^+$ 351.1646, $C_{20}H_{23}N_4{}^{32}S^+$ required 351.1643.

5.2.6.13. (6R,8S)-6-((1r,3R)-adamantan-1-yl)-8-benzyl-2-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (149)



Following General Procedure 6: benzyl ((1*S*)-1-(1-(2-((1*S*,3*R*)-adamantan-1-yl)-2-oxoethyl)-3-phenyl-1*H*-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **131** (117 mg, 204 μmol), ammonium formate (385 mg, 6.11 mmol) and palladium dihydroxide (29.0 mg, 40.7 μmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v) were used. The crude product was purified by flash column chromatography eluting with 10% ethyl acetate in hexane to yield the title compound **149** as a white solid (79.0 mg, 186 μmol, 91%).

R_f = 0.16 (10% EtOAc in hexane)

$[\alpha]_D^{20}$ = -81.1 (c = 0.3 in CH_3OH)

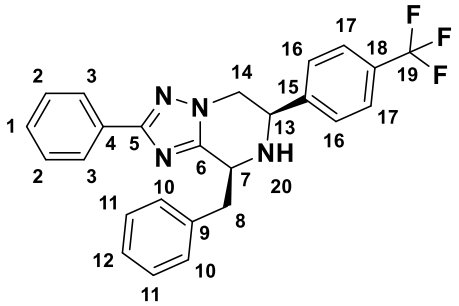
IR: ν_{max} = 2920 (m, C-H), 1703 (m, C=N), 1632 (m, C=C)

^{1}H NMR (400 MHz, d_6-DMSO): δ_H = 8.01 (2H, m, *J* = 4.4 Hz, H3), 7.63 (2H, d, *J* = 7.2 Hz, H11), 7.41 - 7.49 (5H, m, H1, 2 & 10), 7.35 (1H, t, *J* = 7.2 Hz, H12), 5.18 (1H, dd, *J* = 8.7, 3.6 Hz, H7), 4.67 (1H, dd, *J* = 13.6, 4.4Hz, H14a), 4.47 - 4.56 (1H, m, H14b), 3.81 (1H, dd, *J* = 12.1, 4.4 Hz, H13), 3.64 (1H, dd, *J* = 14.3, 3.6 Hz, H8a), 3.54 (1H, dd, *J* = 14.3, 8.7 Hz, H8b), 2.12 - 2.20 (3H, m, H17), 2.00 (3H, d, *J* = 11.9 Hz, H16a), 1.80 - 1.93 (6H, m, H18), 1.77 (3H, d, *J* = 11.9 Hz, H16b)

^{13}C NMR (101 MHz, d_6-DMSO): δ_C = 163.6 (C5), 151.6 (C6), 137.1 (C9), 131.5 (C4), 131.0 (C11), 130.9, (C1), 129.7 (C2), 129.6 (C10), 128.4 (C12), 127.3 (C3), 65.2 (C13), 58.0 (C7), 45.7 (C14), 38.7 (C16), 37.6 (C8), 37.3 (C18), 35.9 (C15), 29.5 (C17)

HRMS (ESI+): found $[M + H]^+$ 425.2684, $C_{28}H_{32}N_4^+$ required 425.2705.

5.2.6.14. (6R,8S)-8-benzyl-2-phenyl-6-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (151)



Following General Procedure 6: benzyl (*S*)-(1-(1-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethyl)-3-phenyl-1*H*-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **133** (66.3 mg, 113 μmol), ammonium formate (215 mg, 3.40 mmol) and palladium dihydroxide (15.9 mg, 22.7 μmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v) were used. The crude product was purified by flash column chromatography eluting with 50% ethyl acetate in hexane to yield the title compound **151** as a white solid (35.0 mg, 80.6 μmol, 71%).

R_f = 0.75 (30% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -45.7 (c = 0.4 in CH_3OH)

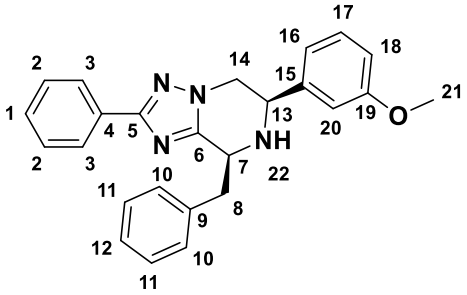
IR: ν_{max} = 2919 (m, C-H), 1702 (m, C=N), 1595 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.10 (2H, d, *J* = 7.9 Hz, H3), 7.89 (2H, d, *J* = 8.2 Hz, H17), 7.85 (2H, d, *J* = 8.2 Hz, H16), 7.53 (2H, d, *J* = 7.3 Hz, H10), 7.48 (3H, dd, *J* = 7.9, 1.2 Hz, H1 & 2), 7.41 (2H, t, *J* = 7.3 Hz, H11), 7.34 (1H, t, *J* = 7.3 Hz, H12), 5.25 (1H, dd, *J* = 8.9, 4.3 Hz, H7), 5.20 (1H, dd, *J* = 11.3, 4.3 Hz, H13), 4.81 (1H, dd, *J* = 13.4, 4.3 Hz, H14a), 4.76 (1H, d, *J* = 13.4, 11.3 Hz, H14b), 3.96 (1H, dd, *J* = 14.8, 4.3 Hz, H8a), 3.44 (1H, dd, *J* = 14.8, 8.9 Hz, H8b)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 163.8 (C5), 151.7 (C6), 136.2 (C15), 133.5 (C9), 133.3 (C18), 131.6 (C4), 131.1 (C1), 131.0 (C10), 130.3, 130.2 (C11 & 17), 129.9 (C2), 129.0 (C12), 127.6, 127.5 (C3 & 16), 124.3 (C19), 59.0 (C13), 58.1 (C7), 50.9 (C14), 38.3 (C8)

HRMS (ESI+): found $[M + H]^+$ 435.1779, $C_{25}H_{22}F_3N_4^+$ required 435.1791.

5.2.6.15. 5.3. (6R,8S)-8-benzyl-6-(3-methoxyphenyl)-2-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (152)



Following General Procedure 6: benzyl (*S*)-(1-(1-(2-(4-methoxyphenyl)-2-oxoethyl)-3-phenyl-1*H*-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **134** (100 mg, 183 μmol), ammonium formate (346 mg, 5.49 mmol) and palladium dihydroxide (26.0 mg, 36.9 μmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v) were used. The crude product was purified by flash column chromatography eluting with 20% ethyl acetate in hexane to yield the title compound **152** as a white solid (56.0 mg, 141 μmol, 77%).

R_f = 0.32 (20% EtOAc in hexane)

$[\alpha]_D^{20}$ = -18.2 (c = 0.2 in CH_3OH)

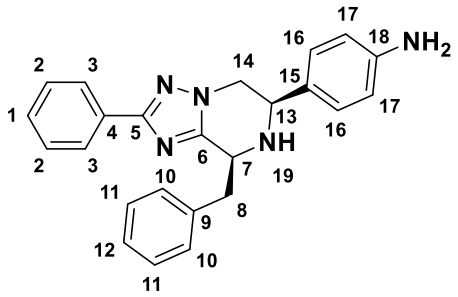
IR: ν_{max} = 2930 (m, C-H), 1678 (m, C=N), 1607 (m, C=C)

^{1}H NMR (400 MHz, CD_3OD): δ_H = 8.03 - 8.14 (2H, m, H3), 7.55 (2H, d, *J* = 7.5 Hz, H10), 7.44 - 7.50 (3H, m, H1 & 2), 7.37 - 7.43 (4H, m, H11, 17 & 20), 7.32 (1H, t, *J* = 7.2 Hz, H12), 7.28 (1H, d, *J* = 7.2 Hz, H16), 7.06 (1H, d, *J* = 8.2 Hz, H18), 5.27 - 5.29 (1H, m, H7), 5.14 (1H, d, *J* = 8.2 Hz, H13), 4.76 (1H, d, *J* = 13.6 Hz, H14b), 3.95 (1H, d, *J* = 14.6 Hz, H8a), 3.86 (3H, s, H21), 3.56 (1H, dd, *J* = 14.6, 7.5 Hz, H8b) – H14a obscured by methanol peak

^{13}C NMR (101 MHz, CD_3OD): δ_C = 163.9 (C5), 162.0 (C19), 151.2 (C6), 136.0 (C9), 134.7 (C15), 131.9 (C4), 131.7 (C17), 131.1 (C10), 131.0 (C1), 130.2 (C11), 129.9 (C2), 129.0 (C12), 127.5 (C3), 121.4 (C16), 117.3 (C18), 115.1 (C20), 59.8 (C14), 58.3 (C7), 56.3 (C21), 50.7 (C13), 37.9 (C8)

HRMS (ESI+): found $[M + H]^+$ 397.2018, $C_{25}H_{25}N_4O^+$ required 397.2028.

5.2.6.16. 4-((6R,8S)-8-benzyl-2-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)aniline (154)



Following General Procedure 6: benzyl (*S*)-(1-(1-(2-(4-nitrophenyl)-2-oxoethyl)-3-phenyl-1*H*-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate **136** (68.0 mg, 121 μmol), ammonium formate (229 mg, 3.63 mmol) and palladium dihydroxide (17.0 mg, 24.2 μmol) in ethyl acetate (1 mL), methanol and water (1 mL, 3:1 v:v) were used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in 40-60 petroleum ether to yield the title compound **154** as a white solid (32.6 mg, 85.4 μmol, 71%).

R_f = 0.25 (60% EtOAc in hexane)

$[\alpha]_D^{20}$ = -119.0 (c = 0.2 in CH_3OH)

IR: ν_{max} = 3319 (w, N-H), 2729 (m, C-H), 1518 (C=N), 1491 (m, C=C)

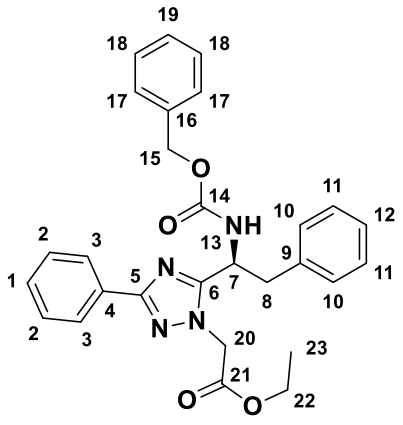
^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.04 - 8.12 (2H, m, H3), 7.86 (2H, d, *J* = 8.5 Hz, H16), 7.53 (2H, d, *J* = 7.5 Hz, H10), 7.49 (2H, d, *J* = 8.5 Hz, H17), 7.43 - 7.48 (3H, m, H1 & 2), 7.39 (2H, t, *J* = 7.5 Hz, H11), 7.32 (1H, t, *J* = 7.5 Hz, H12), 5.23 (1H, dd, *J* = 9.2, 4.8 Hz, H7), 5.16 (1H, dd, *J* = 10.4, 6.0 Hz, H13), 4.73 - 4.83 (2H, m, H14), 3.94 (1H, dd, *J* = 14.7, 4.8 Hz. H8a), 3.48 (1H, dd, *J* = 14.7, 9.2 Hz, H8b)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 163.8 (C5), 151.5 (C6), 144.7 (C18), 136.2 (C9), 131.6 (C4), 131.6 (C16), 131.1 (C1), 131.1 (C10), 130.3 (C11), 129.9 (C2), 129.4 (C15), 129.0 (C12), 127.6 (C3), 124.6 (C17), 58.9 (C13), 58.1 (C7), 50.7 (C14), 38.2 (C8)

HRMS (ESI+): found $[M + H]^+$ 382.2050, $C_{24}H_{24}N_5^+$ required 382.2032.

5.3. Efficient Synthesis of 1,2,4-Triazole heterocycles: Studies towards *trans*-diastereomers

5.3.1. Ethyl (S)-2-(5-(1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-1-yl)acetate (164)



Following General Procedure 5: benzyl ((3-phenyl-1*H*-1,2,4-triazol-5-yl)methyl)carbamate **54** (900 mg, 2.26 mmol), ethyl 2-bromoacetate (300 μL, 2.71 mmol) and potassium carbonate (312 mg, 2.26 mmol) in DMF (3 mL) were used. The crude product was purified by flash column chromatography eluting with 20% ethyl acetate in 40-60 petroleum ether to yield the title compound **164** as a white solid (1.08 g, 2.25 mmol, 99%).

R_f = 0.42 (10% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -14.6 (c = 0.1 in $CHCl_3$)

IR: ν_{max} = 3675 (m, N-H), 2988 (s, C-H), 2901 (s, C-H), 1743 (s, C=O), 1697 (s, C=O), 1406 (m, C=C), 1394 (m, C=C), 1382 (m, C=C)

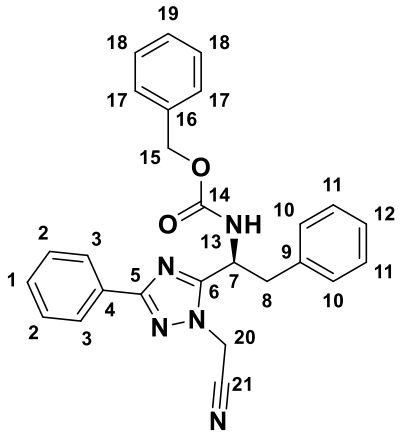
^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.08 (2H, dd, *J* = 8.0, 1.5 Hz, H3), 7.39 - 7.49 (4H, m, H1, 2 & 19), 7.28 - 7.37 (7H, m, H11, 12, 17 & 18), 7.16 (2H, dd, *J* = 7.5, 1.4 Hz, H10), 5.59 (1H, d, *J* = 8.5 Hz, H13), 5.09 (1H, d, *J* = 12.3 Hz, H20a), 5.04 (1H, t, *J* = 7.5 Hz, H7), 5.03 (2H, d, *J* = 12.3 Hz, H20b), 4.92 (1H, d, *J* = 17.7 Hz, H15a), 4.53 (1H, d, *J* = 17.7 Hz, H15b), 4.19 (2H, q, *J* = 7.0 Hz, H22), 3.37 (1H, dd, *J* = 14.0, 7.5 Hz, H8a), 3.30 (1H, dd, *J* = 14.0, 7.5 Hz, H8b), 1.25 (3H, t, *J* = 7.0 Hz, H23)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 166.9 (C21), 166.8 (C5), 161.4 (C6), 156.8 (C14), 136.3 (C9), 136.0 (C16), 130.6 (C4), 129.3 (C1), 129.3 (C10), 128.7, 128.5 (C11 & 18), 128.5 (C2), 128.2 (C19), 127.9

(C17), 127.1 (C12), 126.4 (C3), 67.1 (C7/20), 62.2 (C22), 49.5 (C7/20), 48.6 (C15), 40.8 (C8), 14.0 (C23)

HRMS (ESI+): found $[M + H]^+$ 485.2189, $C_{28}H_{29}N_4O_4^+$ required 285.2189.

5.3.2. Benzyl (S)-(1-(1-(cyanomethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (168)



Following General Procedure 5: benzyl ((3-phenyl-1*H*-1,2,4-triazol-5-yl)methyl)carbamate **54** (850 mg, 2.13 mmol), bromoacetonitrile (180 µL, 2.56 mmol) and potassium carbonate (295 mg, 2.13 mmol) in DMF (3 mL) were used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in 40-60 petroleum ether to yield the title compound **168** as a white solid (825 mg, 1.89 mmol, 89%).

R_f = 0.33 (30% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +10.9 (c = 0.1 in $CHCl_3$)

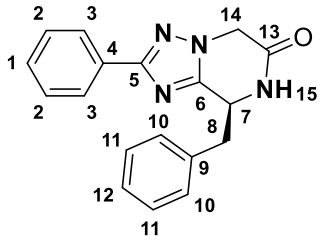
IR: ν_{max} = 3320 (m, C-H), 2158 (m, C≡N), 1686 (s, C=O), 1531 (s, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.24 (1H, d, *J* = 7.9 Hz, H13), 8.01 (2H, d, *J* = 6.7 Hz, H3), 7.45 - 7.53 (3H, m, H1 & 2), 7.24 - 7.35 (7H, m, H10, 11, 18 & 19), 7.22 (3H, d, *J* = 7.3 Hz, H12 & 17), 5.60 (1H, d, *J* = 17.8 Hz, H20a), 5.55 (1H, d, *J* = 17.8 Hz, H20b), 5.22 (1H, dd, *J* = 9.2, 7.9 Hz, H7), 4.99 (1H, d, *J* = 12.6 Hz, H15a), 4.93 (1H, d, *J* = 12.6 Hz, H15b), 3.26 (2H, d, *J* = 9.2 Hz, H8)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 160.7 (C5), 157.9 (C6), 156.1 (C14), 137.1 (C9), 136.7 (C16), 130.1 (C4), 129.8 (C1), 129.4 (C11), 129.0 (C2), 128.4, 128.3 (C10 & 18), 127.9 (C19), 127.6 (C17), 126.7 (C12), 125.9 (C3), 115.0 (C21), 65.7 (C15), 47.5 (C7), 37.9 (C8), 36.5 (C20)

HRMS (ESI+): found $[M + H]^+$ 438.1941, $C_{26}H_{24}N_5O_2^+$ required 438.1930.

5.3.3. (S)-8-benzyl-2-phenyl-7,8-dihydro-[1,2,4]triazolo[1,5-a]pyrazin-6(5H)-one (167)



To a stirred solution of ethyl (*S*)-2-(5-(1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)-3-phenyl-1*H*-1,2,4-triazol-1-yl)acetate **164** (318 mg, 0.661 mmol, 1.0 eq.) in methanol (7.0 mL, 0.1 M) was added the palladium on carbon catalyst (10%, 108 mg, 10% w/w, 10 mol%). The reaction was stirred under hydrogen atmosphere for 3 h. The catalyst was removed by filtration through Celite® and washed with hot methanol (3 x 30 mL). The combined filtrates were concentrated under reduced pressure. The resultant crude compound was purified by flash column chromatography on silica eluting with 0-100% ethyl acetate in 40-60 petroleum ether to yield the title compound **167** as a white solid (165 mg, 0.954 mmol, 82%).

R_f = 0.46 (EtOAc)

$[\alpha]_D^{20}$ = -138.5 (c = 0.1 in $CHCl_3$)

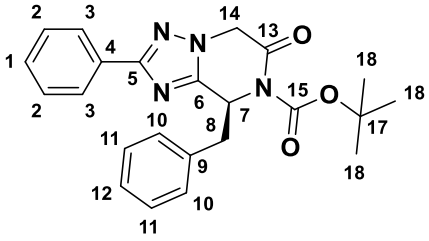
IR: ν_{max} = 2962 (m, C-H), 1673 (s, C=O), 1629 (s, C=O), 1439 (s, C=C)

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.13 (2H, dd, *J* = 7.9, 1.5 Hz, H3), 7.44 - 7.54 (3H, m, H1 & 2), 7.27 - 7.36 (3H, m, H11 & 12), 7.03 - 7.09 (2H, m, H10), 6.96 (1H, br s, H15), 5.16 - 5.19 (1H, m, H7), 4.67 (1H, dd, *J* = 18.0, 1.5 Hz, H14a), 4.03 (1H, d, *J* = 18.0 Hz, H14b), 3.45 (1H, dd, *J* = 13.7, 3.8 Hz, H8a), 3.26 (1H, dd, *J* = 13.7, 6.1 Hz, H8b)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 165.0 (C13), 163.3 (C6), 149.6 (C5), 133.9 (C9), 130.4 (C4), 129.8 (C10), 129.7 (C1), 128.9 (C11), 128.7 (C2), 127.8 (C12), 126.4 (C3), 51.5 (C7), 48.9 (C14), 42.4 (C8)

HRMS (ESI+): found $[M + H]^+$ 305.1403, $C_{18}H_{17}N_4O^+$ required 305.1402.

5.3.4. tert-butyl (S)-8-benzyl-6-oxo-2-phenyl-5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazine-7(8H)-carboxylate (170)



To a stirred solution (*S*)-8-benzyl-2-phenyl-7,8-dihydro-[1,2,4]triazolo[1,5-a]pyrazin-6(5*H*)-one **167** (18.0 mg, 0.060 mmol, 1.0 eq.) in acetonitrile (0.90 mL, 0.3 M) were successively added DMAP (4.00 mg, 0.030 mmol, 0.5 eq.) and di-*tert*-butyl dicarbonate (19.0 mg, 0.090 mmol, 1.5 eq.) and the mixture was stirred at rt for 1 h. The solvent was removed under reduced pressure. The resultant crude compound was purified by flash column chromatography on silica eluting with 35% diethyl ether in 40-60 petroleum ether to yield the title compound **170** as a white solid (21.0 mg, 0.050 mmol, 88%).

R_f = 0.44 (30% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -56.0 (c = 0.1 in CH_3OH)

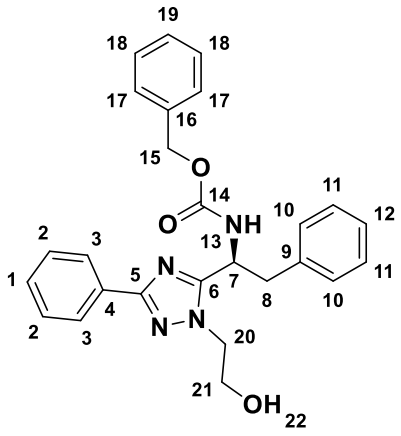
IR: ν_{max} = 2962 (m, C-H), 1764 (s, C=O), 1694 (s, C=O), 1623 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 8.12 (2H, dd, *J* = 8.1, 1.4 Hz, H3), 7.44 - 7.53 (3H, m, H1 & 2), 7.32 (1H, t, *J* = 7.3 Hz, H12), 7.23 (2H, t, *J* = 7.3 Hz, H11), 6.78 (2H, d, *J* = 7.3 Hz, H10), 5.94 (1H, t, *J* = 3.7 Hz, H7), 4.52 (1H, d, *J* = 18.3 Hz, H14a), 3.54 (1H, dd, *J* = 14.0, 3.7 Hz, H8a), 3.37 (1H, dd, *J* = 14.0, 3.7 Hz, H8b), 3.01 (1H, d, *J* = 18.3 Hz, H14b), 1.65 (9H, s, H18)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 163.3 (C13), 163.2 (C6), 150.7 (C5), 150.3 (C15), 133.5 (C9), 130.4 (C4), 130.3 (C10), 129.7 (C1), 129.0 (C11), 128.7 (C2), 128.1 (C12), 126.4 (C3), 85.3 (C17), 54.8 (C7), 49.9 (C14), 41.2 (C8), 28.0 (C18)

HRMS (ESI+): found $[M + H]^+$ 405.1931, $C_{23}H_{25}N_4O_3^+$ required 405.1927.

5.3.5. Benzyl (S)-(1-(1-(2-hydroxyethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (174)



To a stirred solution of ethyl (*S*)-2-(5-(1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)-3-phenyl-1*H*-1,2,4-triazol-1-yl)acetate **164** (700 mg, 1.44 mmol, 1.0 eq.) in ethanol (9.0 mL, 0.2 M) at 0 °C, was added lithium borohydride (2.63 mL, 2.63 mmol, 1.8 eq.). The reaction was stirred at room temperature for 18 h before it was quenched with a saturated aqueous solution of ammonium chloride (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure. The resultant crude compound was purified by flash column chromatography on silica eluting with 0-100% ethyl acetate in 40-60 petroleum ether to yield the title compound **174** as a white solid (578 mg, 1.31 mmol, 91%).

R_f = 0.57 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +53.3 (c = 0.2 in $CHCl_3$)

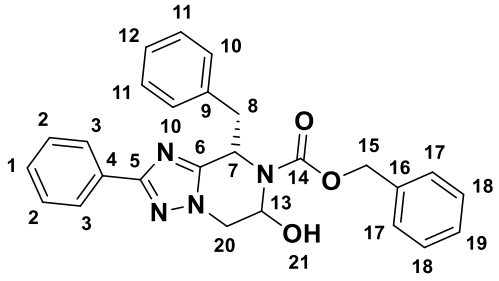
IR: ν_{max} = 3676 (m, O-H), 2988 (s, C-H), 2901 (s, C-H), 1697 (m, C=O), 1406 (m, C=C), 1394 (m, C=C), 1382 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.16 (1H, d, *J* = 8.5 Hz, H13), 7.99 (2H, d, *J* = 7.0 Hz, H3), 7.46 (2H, t, *J* = 7.0 Hz, H2), 7.40 (1H, t, *J* = 7.0 Hz, H1), 7.30 - 7.34 (2H, m, H11), 7.24 - 7.29 (5H, m, H10, 18 & 19), 7.18 - 7.23 (3H, m, H12 & 17), 5.13 (1H, ddd, *J* = 9.8, 8.5, 5.2 Hz, H7), 5.10 (1H, t, *J* = 5.3 Hz, H22), 4.95 (1H, d, *J* = 12.8 Hz, H15a), 4.90 (2H, d, *J* = 12.8 Hz, H15b), 4.42 (1H, ddd, *J* = 14.1, 8.9, 5.0 Hz, H20a), 4.16 (1H, dt, *J* = 14.1, 4.1 Hz, H20b), 3.71 - 3.78 (1H, m, H21a), 3.61 - 3.65 (1H, m, H21b), 3.23 (1H, dd, *J* = 13.7, 9.8 Hz, H8a), 3.15 (1H, dd, *J* = 13.7, 5.2 Hz, H8b)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 159.7 (C5), 157.7 (C6), 155.9 (C14), 137.9 (C9), 136.9 (C16), 131.1 (C4), 129.4 (C11), 129.0 (C1), 128.7 (C2), 128.3, 128.1 (C10 & 18), 127.7 (C19), 127.4 (C17), 126.4 (C12), 125.6 (C3), 65.4 (C15), 59.7 (C21), 50.5 (C20), 48.0 (C7), 38.6 (C8)

HRMS (ESI+): found $[M + H]^+$ 443.2071, , $C_{26}H_{27}N_4O_3^+$ required 443.2083.

5.3.6. Benzyl 8-benzyl-6-hydroxy-2-phenyl-5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazine-7(8H)-carboxylate (175)



A stirred solution of ethyl (*S*)-2-(5-(1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)-3-phenyl-1*H*-1,2,4-triazol-1-yl)acetate **174** (300 mg, 0.681 mmol, 1.0 eq.) and 2-iodoxybenzoic acid (570 mg, 2.03 mmol, 3.0 eq.) in ethyl acetate (7.0 mL, 0.1 M) was heated to reflux for 12 hours. The reaction mixture was quenched with water, filtered through Celite®, and then extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed brine (10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure. The resultant crude compound was purified by flash column chromatography on silica eluting with 0-100% ethyl acetate in 40-60 petroleum ether to yield the title compound **175** as a white solid (298 mg, 0.681 mmol, 99%).

R_f = 0.50 & 0.61 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +4.0 (c = 0.1 in $CHCl_3$)

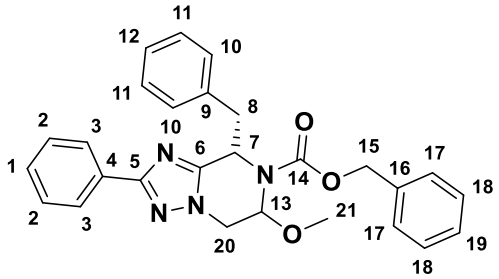
IR: ν_{max} = 2962 (m, C-H), 1709 (s, C=O)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.07 - 8.17 (6H, m, H1a/b, 3a, 3b), 7.62 (1H, tt, *J* = 7.4 Hz, H1a/b), 7.29 - 7.54 (13H, m, H2a, 2b, 17a, 17b, 18a, 18b, 19a & 19b), 7.19 - 7.27 (6H, m, H10a/b, 11a/b,12a & 12b), 7.15 (2H, t, *J*=7.9 Hz, H11a/b), 6.64 (2H, d, *J* = 7.0 Hz, H10a/b), 6.37 - 6.39 (1H, m, H13a), 5.75 (1 H, t, *J* = 0.9 Hz, H13b), 5.71 (1H, t, *J* = 3.1 Hz, H7a), 5.61 (1H, dd, *J* = 4.4, 2.7 Hz, H7b), 5.39 (2H, s, H15b), 5.04 (1H, d, *J*=11.7, H15aa), 4.51 (1H, d, *J* = 11.7, H15ab), 4.34 (2H, s, H20a), 4.01 (2H, d, *J* = 13.4 Hz, H8aa), 3.53 3.65 (1H, m, H8ba), 3.44 (2H, s, H20b), 3.19 (1H, dd, *J*=13.7, 2.7 Hz, H8bb), 2.35 (1 H, dd, *J*=13.4, 3.1 Hz, H8ab)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 170.2, 170.2 (C5a & 5b), 162.2, 162.1 (C6a & 6b), 151.7, 151.7 (C14a & 14b), 137.6, 137.0 (C9a & 9b), 135.4, 135.4 (C16a & 16b), 133.7 (C1a/b), 130.8, 130.7 (C4a & 4b), 130.2 (C1a/b), 130.1, 129.9 (C10a & 10b), 129.4, 129.4 (C2a & 2b), 129.3, 128.9, 128.8, 128.6, 128.4, 128.3 (C17a, 17b, 18a, 18b, 19a & 19b), 128.5, 128.5 (C11a & 11b), 127.4, 127.4 (C12a & 12b), 126.4, 126.4 (C3a & 3b), 74.9 (C13b), 73.7 (C13a), 68.6 (C15b), 68.3 (C15a), 53.4 (C7a), C53.4 (C7b), 51.5 (C20a), 51.1 (C20b), 49.4 (C8a), 49.4 (C8b)– ratio of diastereomers 1:1

HRMS (ESI+): found $[M + H]^+$ 441.1926, $C_{26}H_{25}N_4O_3^+$ required 441.1927.

5.3.7. Benzyl (8S)-8-benzyl-6-methoxy-2-phenyl-5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazine-7(8H)-carboxylate (177)



A solution of benzyl 8-benzyl-6-hydroxy-2-phenyl-5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazine-7(8*H*)-carboxylate **175** (100 mg, 0.231 mmol, 1.0 eq.) and *p*-toluene sulfonic monohydrate (6.00 mg, 230 μmol, 0.1 eq.) in methanol (1.0 mL, 0.1 M) was stirred at room temperature for 18 hours. The reaction mixture was quenched by addition of a saturated aqueous solution of sodium hydrogen carbonate (5 mL) and extracted with diethyl ether (3 x 5 mL). The solvent was removed under reduced pressure. The resultant crude compound was purified by flash column chromatography on silica eluting with 0-100% ethyl acetate in 40-60 petroleum ether to yield the title compound **177** as a white solid (68.0 mg, 0.151 mmol, 65%).

R_f = 0.36 & 0.45 (30% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -0.6 (c = 0.2 in $CHCl_3$)

IR: ν_{max} = 2944 (m, C-H), 1703 (s, C=O)

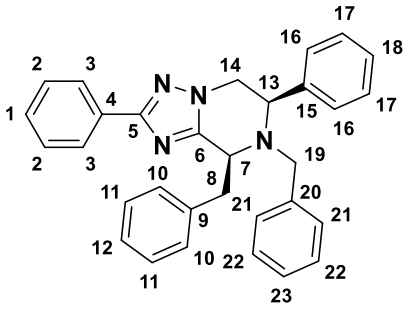
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.12 (2H, dd, *J* = 8.1, 1.4 Hz, H3), 8.02 (3H, d, *J* = 7.0 Hz, H3), 7.28 - 7.52 (25H, m, H1 & 2, 10, 11, 12, 17, 18 & 19), 7.19 (1H, t, *J* = 7.0 Hz, H12), 7.10 (2H, t, *J* = 7.0 Hz, H11), 6.53 (2H, d, *J* = 7.0 Hz, H10), 6.05 (1H, d, *J* = 3.1 Hz, H13), 5.65 (1H, t, *J* = 6.9 Hz, H7), 5.51 (1.5H, dd, *J* = 4.6, 2.4 Hz, H7), 5.38 (1H, d, *J* = 10.4 Hz, H15a), 5.09 (1.5H, d, *J* = 11.6 Hz, H15a),

4.55 - 4.64 (3H, m, H20), 4.30 (2H, dd, *J* = 13.0, 3.1 Hz, H20), 3.99 (3H, dd, *J* = 10.4, 1.5 Hz, H15b), 3.56 (4.5H, s, H21), 3.45 (1H, dd, *J* = 13.7, 5.8 Hz, H8a), 3.33 (3H, br s, H21), 3.10 - 3.29 (4H, m, H8) – ratio of diastereomers 1:1.5

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 162.0 (C5), 155.4 (C6), 151.4 (C14), 137.5 (C9), 135.7 (C4), 135.2 (C16), 130.9 (C1), 129.9, 129.8 (C10), 128.7 (C19), 128.6 (C18), 128.5 (C2), 128.2(C11), 127.2 (C12), 126.7 (C17), 126.3 (C3), 80.9 (C13), 68.2 (C15), 56.7 (C21), 53.6 (C7), 50.9 (C20), 42.6 (C8)

HRMS (ESI+): found $[M + H]^+$ 455.2085, $C_{27}H_{27}N_4O_3^+$ required 455.2083.

5.3.8. (6R,8S)-8-benzyl-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (180)



A solution of (6*R*,8*S*)-8-benzyl-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine **58** (100 mg, 0.270 mmol, 1.0 eq.), benzyl bromide (90.0 µL, 0.811 mmol, 3.0 eq.) and potassium carbonate (111 mg, 0.811 mmol, 3.0 eq.) in DMF (1 mL, 0.2 M) was stirred at room temperature for 18 hours. The reaction was quenched with water and extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure. The resultant crude compound was purified by flash column chromatography on silica eluting with 0-100% ethyl acetate in 40-60 petroleum ether to yield the title compound **180** as a yellow solid (27.0 mg, 69.0 µmol, 25%, 95% BRSM).

R_f = 0.40 (30% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -79.2 (c = 0.2 in $CHCl_3$)

IR: ν_{max} = 2925 (m, C-H), 2854 (m, C-H), 1701 (m, C=C), 1493 (m, C=C)

^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 8.10 (2H, d, *J* = 7.0 Hz, H3), 7.27 - 7.47 (12H, m, H1, 2, 11, 16, 17, 22, 23), 7.18 - 7.24 (4H, m, H12, 18 & 21), 6.92 (2H, dd, *J* = 7.5, 1.7 Hz, H10), 4.73 (1H, t, *J* = 4.6

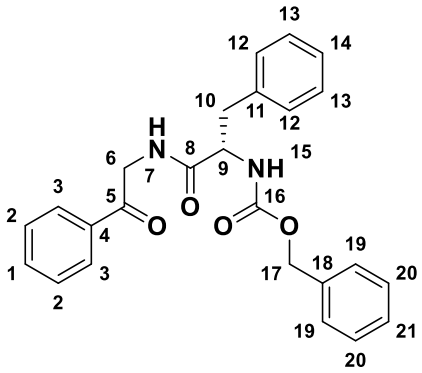
Hz, H7), 4.09 (1H, t, *J* = 9.2 Hz, H13), 4.05 (1H, dd, *J* = 12.8, 9.2 Hz, H14a), 4.01 (1H, d, *J* = 14.3 Hz, H19a), 3.72 (1H, d, *J* = 14.3 Hz, H19b), 3.30 (1H, dd, *J* = 12.8, 9.2 Hz, H14b), 2.97 (2H, d, *J* = 4.6 Hz, H8)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 161.5 (C5), 154.2 (C6), 139.6 (C15), 137.1 (C9), 136.8 (C20), 131.0 (C4), 130.2 (C10), 129.9 (C21), 129.2 (C1), 129.0 (C2), 128.5 (C17), 128.4 (C16), 128.2 (C18), 127.8 (C22), 127.7 (C23), 127.0 (C12), 126.6 (C11), 126.3 (C3), 61.3 (C13), 57.7 (C7), 56.4 (C19), 50.6 (C14), 40.4 (C8)

HRMS (ESI+): found $[M + H]^+$ 457.2393, $C_{31}H_{29}N_4^+$ required 457.2392.

5.4. Efficient Synthesis of 1,3-Imidazole Heterocycles

5.4.1. Benzyl (S)-(1-oxo-1-((2-oxo-2-phenylethyl)amino)-3-phenylpropan-2-yl)carbamate (192)



To a stirred solution of 2-aminoacetophenone hydrochloride **184** (2.00 g, 11.7 mmol, 1.0 eq.) and Cbz-*L*-phenylalanine **49** (3.49 g, 11.7 mmol, 1.0 eq.) in dichloromethane (100 mL, 0.1 M) was added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (2.35 g, 12.2 mmol, 1.05 eq.), *N*-methylmorpholine (1.35 mL, 12.2 mmol, 1.05 eq.) and 1-hydroxy-7-azabenzotriazole (1.66 g, 12.2 mmol, 1.05 eq.) at 0 ^{o}C. The reaction mixture was then stirred at room temperature for 3 hours. Upon completion the reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate solution and extracted with dichloromethane (3 x 150 mL). The combined organic fractions were washed with brine (50 mL) and dried ($MgSO_4$) before the solvent was removed under reduced pressure to yield the crude compound. The resultant crude product was purified by flash column chromatography on silica eluting with 0-100% ethyl acetate in 40-60 petroleum ether to yield the title compound **192** as a yellow solid (4.44 g, 11.7 mmol, 100%).

R_f = 0.20 (30% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -15.8 (c = 1.0 in CH_3OH)

IR: ν_{max} = 3675 (m, N-H), 3298 (m, N-H), 2988 (s, C-H), 2901 (s, C-H), 1694 (s, C=O), 1644 (s, C=O), 1597 (m, C=C), 1531 (m, C=C), 1494 (m, C=C), 1448 (m, C=C)

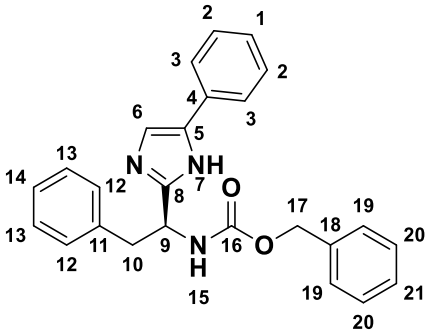
^{1}H NMR (400 MHz, d_6-DMSO): δ_H = 8.43 (1H, t, *J* = 5.4 Hz, H7), 8.01 (1H, d, *J* = 7.4 Hz, H3), 7.68 (1H, t, *J* = 7.4 Hz, H1), 7.57 (2H, q, *J* = 7.4 Hz, H2 & 15), 7.12 - 7.38 (10H, m, H12, 13, 14, 19, 20 & 21), 4.94 (2H, s, H17), 4.71 (1H, dd, *J* = 18.5, 5.4 Hz, H6a), 4.71 (1H, dd, *J* = 18.5, 5.4 Hz, H6b), 4.37 (1H, ddd, *J* = 11.2, 8.8, 3.5 Hz, H9), 3.09 (1H, dd, *J* = 13.7, 3.5 Hz, H10a), 2.77 (1H, dd, *J* = 13.7, 11.2 Hz, H10b)

^{13}C NMR (101 MHz, d_6-DMSO): δ_C = 195.2 (C5), 172.2 (C8), 156.0 (C16), 138.4 (C11), 137.1 (C18), 135.0 (C4), 133.7 (C1), 128.9 (C2), 129.3, 128.4, 128.2, 127.7 (C12, 13, 20 & 21), 127.9 (C3), 127.5 (C19), 126.3 (C14), 65.3 (C17), 56.3 (C9), 46.1 (C6), 46.1 (C10)

HRMS (ESI+): found $[M + H]^+$ 417.1796, $C_{25}H_{25}N_2O_4^+$ required 417.1814

This data is in accordance with that previously reported.[249]

5.4.2. Benzyl (S)-(2-phenyl-1-(5-phenyl-1H-imidazol-2-yl)ethyl)carbamate (193)



A solution of benzyl (*S*)-(1-oxo-1-((2-oxo-2-phenylethyl)amino)-3-phenylpropan-2-yl)carbamate **192** (1.00 g, 2.40 mmol, 1.0 eq.) and ammonium acetate (1.85 g, 24.0 mmol, 10.0 eq.) in xylene (8 mL, 0.3 M) was refluxed using Dean-Stark apparatus. After complete consumption of the starting material, the reaction mixture was concentrated. The residue was re-dissolved in dichloromethane, washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure. The resultant crude compound was purified by flash column chromatography on silica eluting with 0-100% ethyl acetate in 40-60 petroleum ether to yield the title compound **193** as an orange solid (768 mg, 1.93 mmol, 81%).

R_f = 0.41 (40% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -0.1 (c = 0.7 in CH_3OH)

IR: ν_{max} = 3675 (m, N-H), 2988 (s, C-H), 2901 (s, C-H), 1690 (m, br, C=O), 1494 (m, C=C), 1453 (m, C=C), 1406 (m, C=C)

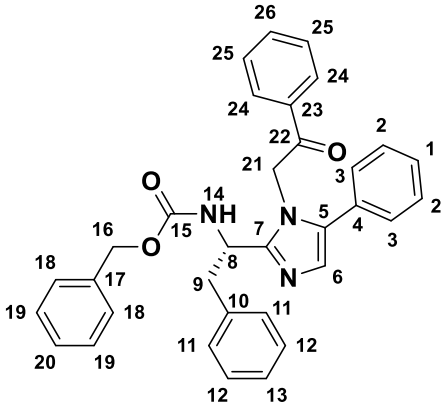
^{1}H NMR (500 MHz, d_6-DMSO): δ_H = 11.96 (1H, br s, H7), 7.81 (1H, d, *J* = 8.9 Hz, H15), 7.78 (2H, d, *J* = 7.3 Hz, H3), 7.63 (1H, d, *J* = 7.3 Hz, H21), 7.51 (1H, d, *J* = 1.5 Hz, H6), 7.39 (1H, t, *J* = 7.8 Hz, H14), 7.29 - 7.37 (4H, m, H2 & 20), 7.15 - 7.28 (7H, m, H1, 12, 13, 19), 5.02 (1H, d, *J* = 12.8 Hz, H17a), 4.96 (1H, d, *J* = 12.8 Hz, H17b), 4.93 (1H, ddd, *J* = 9.3, 8.9, 5.8 Hz, H9), 3.31 (1H, dd, *J* = 13.6, 5.8 Hz, H10a), 3.06 (1H, dd, *J* = 13.6, 9.3 Hz, H10b)

^{13}C NMR (126 MHz, d_6-DMSO): δ_C = 156.2 (C16), 149.0 (C8), 140.0 (C5), 138.8 (C11), 137.6 (C18), 135.4 (C4), 129.7 (C13), 129.3 (C14), 128.8 (C2), 128.7, 128.5 (C12 & 19), 127.8 (C20), 126.7 (C21), 126.3 (C1), 124.7 (C3), 113.0 (C6), 65.6 (C17), 51.5 (C9), 39.5 (C10)

HRMS (ESI+): found $[M + H]^+$ 398.1865, $C_{25}H_{24}N_3O_2^+$ required 398.1869

This data is in accordance with that previously reported.[249]

5.4.3. Benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-5-phenyl-1H-imidazol-2-yl)-2-phenylethyl)carbamate (194)



Following General Procedure 5: benzyl (*S*)-(2-phenyl-1-(5-phenyl-1*H*-imidazol-2-yl)ethyl)carbamate **193** (200 mg, 0.501 mmol), 2-bromoacetophenone (105 mg, 0.531 mmol) and potassium carbonate (70.0 mg, 0.501 mmol) in DMF (2 mL) were used. The crude product was purified by flash column chromatography on silica eluting with 50% ethyl acetate in 40-60 petroleum ether to yield the title compound **194** as a pale yellow solid (202 mg, 0.391 mmol, 78%).

R_f = 0.44 (30% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -18.8 (c = 0.4 in CH_3OH)

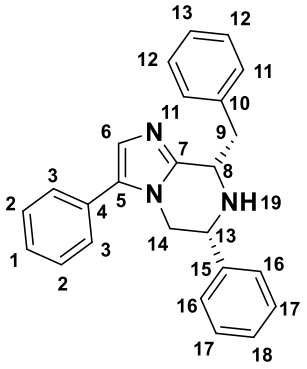
IR: ν_{max} = 2927 (m, C-H), 1689 (S, C=O), 1684 (s, C=O), 1521 (m, C=C), 1496 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.87 (2H, d, *J* = 7.3 Hz, H24), 7.79 (2H, dd, *J* = 8.2, 1.2 Hz, H3), 7.65 (1H, tt, *J* = 7.3, 1.2 Hz, H26), 7.51 (2H, t, *J* = 7.3 Hz, H25), 7.37 - 7.41 (3H, m, H2 & 20), 7.28 - 7.33 (3H, m, H1 & 18), 7.20 - 7.26 (H, m, H11, 13 & 19), 7.16 (2H, t, *J* = 5.8 Hz, H12), 7.05 (1H, s, H6), 5.84 (1H, d, *J* = 7.3 Hz, H14), 5.17 (1H, d, *J* = 18.3 Hz, H21a), 5.03 - 4.96 (2H, m, H16a & 21b),4.85 - 4.92 (2H, m, H8 & 16b), 3.34 - 3.45 (2H, m, H9)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 191.6 (C22), 155.8 (C15), 148.0 (C7), 140.7 (C5), 137.4 (C10), 136.3 (C17), 134.2, 134.1, 134.0 (C4, 23 & 26), 129.6 (C12), 129.0 (C25), 128.5, 128.5, 128.5 (C2, 11 & 19), 128.2, (C20), 128.0 (C24), 127.8 (C18), 126.8, 126.7 (C1 & 13), 125.0 (C3), 116.7 (C6), 66.7 (C16), 51.4 (C21), 49.2 (C8), 41.3 (C9)

HRMS (ESI+): found $[M + H]^+$ 516.2271, $C_{33}H_{30}N_3O_3^+$ required 516.2287.

5.4.4. (6S,8R)-8-benzyl-3,6-diphenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine (195)



Following the General Procedure 6: benzyl (*S*)-(1-(1-(2-oxo-2-phenylethyl)-5-phenyl-1*H*-imidazol-2-yl)-2-phenylethyl)carbamate **194** (93.0 mg, 0.181 mmol), ammonium formate (341 mg, 5.42 mmol) and palladium dihydroxide (25.0 mg, 36.0 μmol) in ethyl acetate (1 mL) and methanol and water (1 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in 40-60 petroleum ether to yield the title compound **195** as a yellow solid (46.0 mg, 130 μmol, 74%).

R_f = 0.44 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +82.9 (c = 0.1 in CH_3OH)

IR: ν_{max} = 2974 (m, C-H), 1713 (s, C=N), 1521 (m, C=C), 1485 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 7.98 (1H, s, H6), 7.83 (2H, d, *J* = 7.3 Hz, H3), 7.71 (2H, d, *J* = 6.4 Hz, H16), 7.56 - 7.62 (2H, m, H2), 7.52 - 7.56 (3H, m, H1 & 11), 7.45 - 7.52 (3H, m, H17 & 18), 7.40 (2H, t, *J* = 7.5 Hz, H12), 7.33 (1H, t, *J* = 7.6 Hz, H13), 5.33 (1H, d, *J* = 8.3 Hz, H8), 4.62 - 4.76 (2H, m, H14), 3.97 (1H, d, *J* = 13.6 Hz, H9a), 3.65 (1H, dd, *J* = 13.6, 8.3 Hz, H9b)

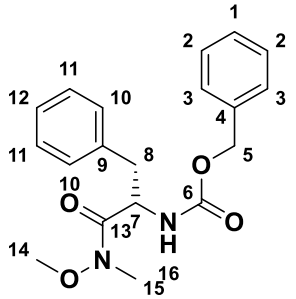
^{13}C NMR (126 MHz, CD_3OD): δ_C = 143.2 (C7), 136.5 (C5), 135.5 (C15), 135.4 (C10), 131.4 (C1), 131.2 (C18), 131.1 (C11), 130.7 (C2), 130.5 (C17), 130.3 (C12), 129.3 (C16), 129.1 (C13), 127.9 (C4), 127.4 (C3), 118.9 (C6), 58.7 (C14), 56.3 (C8), 50.8 (C13), 38.2 (C9)

HRMS (ESI+): found $[M + H]^+$ 366.1953, $C_{25}H_{24}N_3^+$ required 366.1965.

5.5. Efficient Synthesis of 1,2-Pyrazole Heterocycles

5.5.1. Synthesis of the Unsubstituted Pyrazole Scaffold

5.5.1.1. Benzyl (S)-(1-(methoxy(methyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (202)



To a stirred solution of Cbz-*L*-phenylalanine **49** (1.0 g, 3.34 mmol, 1.0 eq.) and N,O-dimethylhydroxylamine hydrochloride (489 mg, 5.01 mmol, 1.5 eq.) in dichloromethane (15 mL, 0.2 M) was added HOBt (496 mg, 3.67 mmol, 1.1 eq.), HBTU (1.39 g, 3.37 mmol, 1.1 eq.) and diisopropylethylamine (1.51 mL, 8.69 mmol, 2.6 eq.). The solution was stirred at room temperature until the starting material had been consumed. The reaction was quenched with saturated aqueous sodium hydrogen carbonate solution (15 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic fractions were washed with brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude compound was purified by flash column chromatography on silica eluting with dichloromethane to yield the title compound **202** as a cloudy liquid (975 mg, 3.34 mmol, 100%).

R_f = 0.53 (Dichloromethane)

$[\alpha]_D^{20}$ = +22.5 (c = 0.2 in $CHCl_3$) - [Literature Value = +20.0 (c = 0.1 in CH_2Cl_2)][305]

IR: ν_{max} = 3305 (m, N-H), 2943 (m, C-H), 1714 (s, C=O), 1650 (s, C=O), 1522 (m, C=C), 1496 (m, C=C)

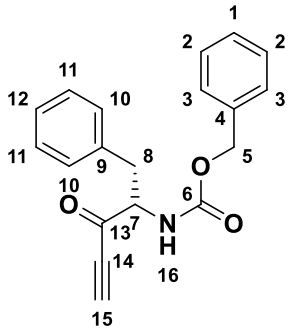
^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.31 - 7.40 (5H, m, H1, 2 & 3), 7.21 - 7.30 (3H, m, H11 & 12), 7.17 (2H, d, *J* = 6.7 Hz, H10), 5.44 (1H, d, *J* = 8.5 Hz, H16), 5.11 (1H, d, *J* = 12.2 Hz, H5a), 4.97 - 5.08 (2H, m, H5b & 7), 3.70 (3H, s, H14), 3.20 (3H, s, H15), 3.10 (1H, dd, *J* = 13.6, 6.0 Hz, H8a), 2.93 (1H, dd, *J* = 13.6, 7.3 Hz, H8b)

^{13}C NMR (101 MHz, d_6-DMSO): δ_C = 171.9 (C13), 156.7 (C6), 155.8 (C9), 136.3 (C4), 129.4 (C11), 128.5, 128.4 (C2 & 10), 128.1 (C1), 128.0 (C3), 126.9 (C12), 66.8 (C5), 61.5 (C7), 52.1 (C15), 38.7 (C8), 32.0 (C14)

HRMS (ESI+): found $[M + H]^+$ 343.1644, $C_{19}H_{22}N_2O_4^+$ required 343.1658

This data is in accordance with that previously recorded.[305]

5.5.1.2. Benzyl (S)-(3-oxo-1-phenylpent-4-yn-2-yl)carbamate (209)



Ethynyl magnesium bromide (9.30 mL, 0.5 M solution in THF, 4.67 mmol, 4.5 eq.) was added dropwise to a stirred solution of benzyl (*S*)-(1-(methoxy(methyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **202** (350 mg, 1.02 mmol, 1.0 eq.) in THF (7.0 mL, 0.15M) at -78 °C. The resulting mixture was stirred at room temperature overnight. After cooling to 0 °C, the reaction was quenched with a saturated aqueous solution of ammonium chloride (10 mL). After stirring for 1 h at room temperature, the reaction was extracted with ethyl acetate (3 x 10 mL); the combined organic fractions were washed with brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude compound was purified by flash column chromatography on silica eluting with 30% ethyl acetate in 40-60 petroleum ether to yield the title compound **209** as a yellow solid (228 mg, 0.741 mmol, 73%).

R_f = 0.58 (25% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +30.8 (c = 0.1 in $CHCl_3$) - [Literature Value = +1.27 (c = 1.1 in $CHCl_3$)][253]

IR: ν_{max} = 3343 (s, N-H), 3032 (m, C≡C-H), 2095 (s, C≡C), 1683 (s, C=O), 1670 (s, C=O), 1531 (s, N-H)

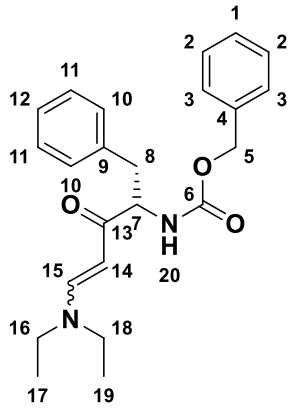
^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.28 - 7.22 (8H, m, H1, 2, 3, 10 & 12), 7.13 (2H, dd, *J* = 7.5, 1.7 Hz, H11), 5.23 (1H, d, *J* = 7.5 Hz, H16), 5.11 (2H, s, H5), 4.74 - 4.84 (1H, m, H7), 3.41 (1H, s, H15), 3.27 - 3.34 (1H, m, H8a), 3.20 - 3.27 (1H, m, H8b)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 184.9 (C13), 155.6 (C6), 136.1 (C4), 134.9 (C9), 129.4 (C11), 128.7, 128.5, 128.3 (C1, 2 & 10), 128.1 (C3), 127.3 (C12), 82.6 (C15), 79.7 (C14), 67.1 (C5), 62.3 (C7), 36.8 (C8)

HRMS (ESI+): found $[M + H]^+$ 308.1298, $C_{19}H_{18}NO_3^+$ required 308.1287

This data is in accordance with that previously recorded.[253]

5.5.1.3. Benzyl (S)-(5-(diethylamino)-3-oxo-1-phenylpent-4-en-2-yl)carbamate (210)



Diethylamine (0.07 mL, 0.70 mmol, 1.1 eq.) was added dropwise to a stirred solution of benzyl (*S*)-(3-oxo-1-phenylpent-4-yn-2-yl)carbamate **209** (196 mg, 0.642 mmol, 1.0 eq.) in dichloromethane (5.0 mL, 0.15 M) at 0 °C. The mixture was stirred at room temperature for 18 hours, before dilution with water (15 mL). The reaction was extracted with dichloromethane (3 x 20 mL) and the combined organic fractions were washed with brine (15 mL), dried (Mg SO_4) and concentrated under reduced pressure. The crude compound was purified by flash column chromatography on silica eluting with 50% ethyl acetate in 40-60 petroleum ether to yield the title compound **210** as a yellow oil (232 mg, 0.611 mmol, 95%).

R_f = 0.40 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +37.0 (c = 0.1 in $CHCl_3$) - [Literature Value = +34.4 (c = 1.1 in $CHCl_3$)][253]

IR: ν_{max} = 2973 (m, C-H), 2934 (m, C-H), 1715 (s, C=O), 1647 (s, C=O), 1555 (s, N-H), 1495 (m, C=C)

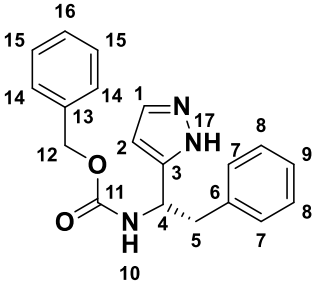
^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.29 - 7.39 (6H, m, H1, 2, 3 & 15), 7.23 - 7.27 (2H, m, H11), 7.13 - 7.23 (3H, m, H10 & 12), 5.84 (1H, d, *J* = 7.2 Hz, H20), 5.11 (2H, s, H5), 4.87 (1H, d, *J* = 12.6 Hz, H14), 4.58 (1H, m, H7), 3.25 (2H, br s, H16/18), 2.95 - 3.12 (4H, m, H8 & 16/18), 1.20 (2H, t, *J* = 6.5 Hz, H17/19), 1.06 (2H, t, *J* = 6.6 Hz, H17/19)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 193.1 (C13), 155.7 (C6), 137.5, 136.8 (C4 & 9), 129.6 (C11), 128.4 (C10), 128.2 (C15), 128.1 (C2), 128.0 (C1), 127.9 (C3), 126.4 (C12), 66.4 (C5), 50.5, 42.6 (C16 & 18), 39.6 (C8), 14.6, 11.4 (C17 & 19) – C7 & 14 obscured by chloroform peak

HRMS (ESI+): found $[M + Na]^+$ 403.2014, $C_{23}H_{28}N_2O_3Na^+$ required 403.1998

This data is in accordance with that previously recorded.[253]

5.5.1.4. Benzyl (S)-(2-phenyl-1-(1H-pyrazol-5-yl)ethyl)carbamate (211)



A solution of benzyl (*S*)-(5-(diethylamino)-3-oxo-1-phenylpent-4-en-2-yl)carbamate **210** (200 mg, 0.530 mmol, 1.0 eq.), hydrazine monohydrate (30.0 µL, 0.551 mmol, 1.1 eq.), and concentrated aqueous hydrochloric acid (37% w/w, 50.0 µL, 0.551 mmol, 1.1 eq.) in ethanol (3 mL, 0.16 M) was refluxed for 3 h. The reaction was cooled to room temperature and the solvent removed under reduced pressure. The resulting residue was diluted with water (10 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude compound was purified by flash column chromatography on silica eluting with 50% ethyl acetate in 40-60 petroleum ether to yield the title compound **211** as a white solid (151 mg, 0.470 mmol, 89%).

R_f = 0.38 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +37.0 (c = 0.1 in $CHCl_3$)

IR: ν_{max} = 3351 (m, N-H), 2920 (m, C-H), 1689 (s, C=O), 1533 (s, N-H)

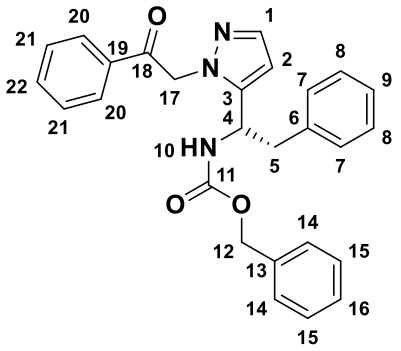
^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.44 (1H, s, H1), 7.27 - 7.38 (6H, m, H14, 15, 16 & 17), 7.14 - 7.24 (3H, m, H8 & 9), 7.08 (2H, d, *J* = 6.6 Hz, H7), 6.06 (1H, s, H2), 5.48 (1H, br s, H10), 5.12 (1H, m, *J* = 6.8 Hz, H4), 5.08 (2H, s, H12), 3.18 (2H, d, *J* = 6.8 Hz, H5)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 155.9 (C11), 148.9 (C3), 137.1 (C6), 136.4 (C13), 129.5 (C1), 128.5, 128.3 (C8 & 15), 128.1 (C7), 127.9 (C16), 126.6 (C14), 124.7 (C9), 103.4 (C2), 66.8 (C12), 50.3 (C4), 41.4 (C5)

HRMS (ESI+): found $[M + H]^+$ 322.1564, $C_{19}H_{20}N_3O_2^+$ required 322.1556

This data is in accordance with that previously recorded.[253]

5.5.1.5. Benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-1H-pyrazol-5-yl)-2-phenylethyl)carbamate (212)



Following General Procedure 5: benzyl (*S*)-(2-phenyl-1-(1*H*-pyrazol-5-yl)ethyl)carbamatete **211** (200 mg, 0.620 mmol), 2-bromoacetophenone **55** (136 mg, 0.681 mmol) and potassium carbonate (86.0 mg, 0.620 mmol) in acetone (2 mL) were used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in 40-60 petroleum ether to yield the title compound **212** as a white solid (174 mg, 0.390 mmol, 64%).

R_f = 0.30 (30% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -13.3 (c = 0.1 in CH_3OH)

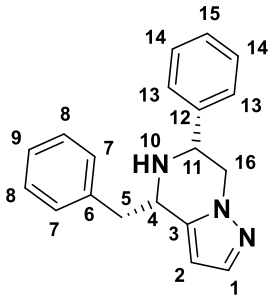
IR: ν_{max} = 2928 (m, C-H), 1702 (s, C=O), 1496 (m, C=C)

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.00 (2H, d, *J* = 7.5 Hz, H20), 7.66 (1H, t, *J* = 7.5 Hz, H21), 7.54 (2H, d, *J* = 7.8 Hz), 7.40 (1H, d, *J* = 2.4 Hz, H1), 7.30 - 7.38 (5H, m, H14, 15 & 16), 7.18 - 7.27 (4H, m, H7, 9 & 10), 7.09 (2H, d, *J* = 6.8 Hz, H8), 6.06 (1H, d, *J*=2.4 Hz, H2), 5.44 (2H, d, *J* = 8.2 Hz, H17), 5.04 - 5.19 (3H, m, H7 & 12), 3.13 - 3.28 (2H, m, H5)

^{13}C NMR (101MHz, $CDCl_3$): δ_C = 191.9 (C18), 155.4 (C11), 152.3 (C3), 137.0 (C16), 136.3 (C13), 134.2 (C19), 133.8 (C1), 131.3 (C20), 129.8 (22), 129.4 (C15), 129.2 (C8), 128.7 (C21), 128.1 (C7), 127.8 (C14), 127.7 (C16), 126.0 (C9), 104.7 (C2), 66.3 (C12), 57.4 (C17), 50.8 (C4), 41.6 (C5)

HRMS (ESI+): found $[M + H]^+$ 440.1969, $C_{27}H_{26}N_3O_3^+$ required 440.1974.

5.5.1.6. (4S,6R)-4-benzyl-6-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (213)



Following General Procedure 6: benzyl (*S*)-(1-(1-(2-oxo-2-phenylethyl)-1*H*-pyrazol-5-yl)-2-phenylethyl)carbamate **212** (14.0 mg, 31.9 μmol), ammonium formate (8.60 mg, 1.37 mmol) and palladium dihydroxide (6.00 mg, 6.37 μmol) in ethyl acetate (1 mL) and methanol and water (1 mL, 3:1 v:v,) was used. The crude product was purified by flash column chromatography eluting with 10% methanol in ethyl acetate to yield the title compound **213** as a white solid (7.00 mg, 26.3 μmol, 82%).

R_f = 0.24 (30% CH_3OH in EtOAc)

$[\alpha]_D^{20}$ = +53.9 (c = 0.2 in CH_3OH)

IR: ν_{max} = 2921 (m, C-H), 1597 (m, N-H)

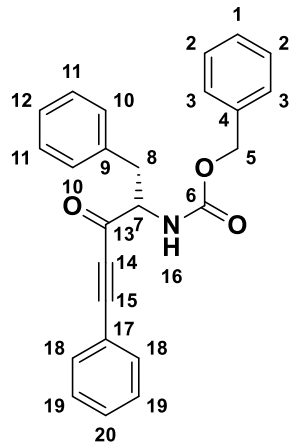
^{1}H NMR (500 MHz, CD_3OD): δ_H = 7.39 - 7.43 (1H, m, H1), 7.21 - 7.35 (8H, m, H7, 9, 13, 14 & 15), 7.17 (2H, d, *J* = 7.9 Hz, H8), 6.12 - 6.16 (1H, m, H2), 5.00 (1H, t, *J* = 5.8 Hz, H11), 4.54 (1H, td, *J* = 7.5, 3.1 Hz, H4), 4.25 - 4.31 (2H, m, H16), 3.20 - 3.24 (2H, m, H5)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 150.4 (C3), 143.2 (C12), 137.5 (C6), 133.7 (C1), 130.7 (C8), 129.9, 129.6 (C7 & 14), 129.1 (C15), 128.4 (C9), 127.3 (C13), 104.8(C2), 74.2 (C15), 60.3 (C16), 52.4 (C4), 41.8 (C5)

HRMS (ESI+): found $[M + H]^+$ 290.1677, $C_{19}H_{19}N_3^+$ required 290.1652.

5.5.2. Synthesis of the Substituted Pyrazole Scaffold

5.5.2.1. Benzyl (S)-(3-oxo-1,5-diphenylpent-4-yn-2-yl)carbamate (214)



Phenylethylene magnesium bromide (8.80 mL, 1 M solution in THF, 8.76 mmol, 4.5 eq.) was added dropwise to a stirred solution of benzyl (*S*)-(1-(methoxy(methyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **202** (1.00 g, 2.92 mmol, 1.0 eq.) in THF (15 mL, 0.15M) at -78 °C. The resulting mixture was stirred at room temperature overnight. After cooling to 0 °C, the reaction was quenched with a saturated aqueous solution of ammonium chloride (10 mL). After stirring for 1 h at room temperature, the reaction mixture was extracted with ethyl acetate (3 x 10 mL); the combined organic fractions were washed with brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude compound was purified by flash column chromatography on silica eluting with 30% ethyl acetate in 40-60 petroleum ether to yield the title compound **214** as a yellow solid (183 mg, 0.470 mmol, 33%).

R_f = 0.25 (10% EtOAc in 40-60 Petroleum Ether)

$[\alpha]_D^{20}$ = -+1.8 (c = 0.1 in $CHCl_3$) - [Literature Value = -26.6 (c = 1.3 in $CHCl_3$)][306]

IR: ν_{max} = 3343 (m, N-H), 2950 (m, C-H), 2206 (m, C≡C), 1702 (s, C=O), 1678 (S, C=O), 1526 (s, N-H), 1494 (m, C=C)

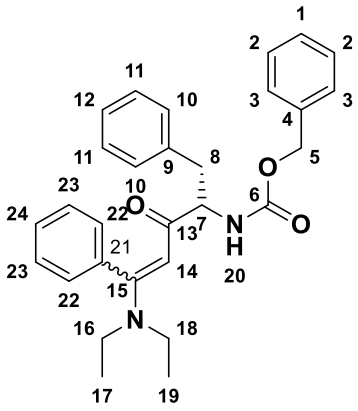
^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.57 (2H, d, *J* = 6.8 Hz, H18), 7.52 (1H, tt, *J* = 7.8, 2.4 Hz, H20), 7.42 (2H, t, *J* = 7.8 Hz, H19), 7.29 - 7.38 (5H, m, H1, 2 & 3), 7.23 - 7.29 (3H, m, H10 & 12), 7.20 (2H, dd, *J* = 8.2, 1.7 Hz, H11), 5.38 (1H, d, *J* = 7.8 Hz, H16), 5.14 (2H, s, H5), 4.90 (1H, dt, *J* = 7.8, 5.8 Hz, H7), 3.34 (2H, d, *J* = 5.8 Hz, H8)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 185.3 (C13), 155.6 (C6), 136.2 (C4), 135.3 (C9), 133.3 (C18), 131.3 (C20), 129.5 (C11), 128.7 (C19), 128.6 (C3), 128.5 (C10), 128.2 (C1), 128.1 (C2), 127.2 (C12), 119.4 (C17), 95.3 (C15), 86.2 (C14), 67.0 (C5), 62.3 (C7), 37.4 (C8)

HRMS (ESI+): found $[M + H]^+$ 384.1584, $C_{25}H_{22}NO_3^+$ required 384.1600

This data is in accordance with that previously reported.[306]

5.5.2.2. Benzyl (S)-(5-(diethylamino)-3-oxo-1,5-diphenylpent-4-en-2-yl)carbamate (215)



Diethylamine (40.0 µL, 0.433 mmol, 1.1 eq.) was added dropwise to a stirred solution of benzyl (*S*)-(3-oxo-1,5-diphenylpent-4-yn-2-yl)carbamate **214** (150 mg, 0.391 mmol, 1.0 eq.) in dichloromethane (1.5 mL, 0.15 M) at 0 °C. The mixture was stirred at room temperature for 18 hours, before dilution with water (15 mL). The reaction was extracted with dichloromethane (3 x 20 mL) and the combined organic fractions were washed with brine (15 mL), dried (Mg SO_4) and concentrated under reduced pressure. The crude compound was purified by flash column chromatography on silica eluting with 50% ethyl acetate in 40-60 petroleum ether to yield the title compound **215** as a yellow oil (193 mg, 0.391 mmol, 100%).

R_f = 0.43 (40% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +0.8 (c = 0.5 in $CHCl_3$)

IR: ν_{max} = 2933 (m, C-H), 1713 (s, C=O), 1641 (m, C=O), 1517 (s, C=C), 1493 (s, C=C)

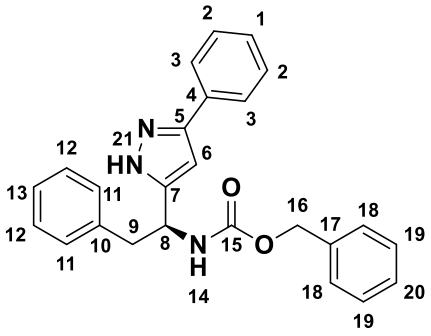
^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.42 - 7.48 (mH, m, H22 & 23), 7.19 - 7.37 (9H, m, H2, 3, 10, 11 & 24), 7.14 (1H, d, *J* = 4.1 Hz, H12), 7.08 (1H, d, *J* = 3.1 Hz, H1), 5.80 (1H, d, *J* = 7.5 Hz, H20), 5.08 (1H, d, *J* = 12.6 Hz, H5a), 5.05 (1H, d, *J* = 12.6 Hz, H5b), 4.90 (1H, s, H14), 4.49 (1H, ddd, *J* = 8.2,

7.5, 5.4 Hz, H7), 3.21 - 2.91 (4H, m, H16 & 18) 3.08 (1H, dd, *J* = 13.5, 5.4 Hz, H8a), 2.93 (1H, dd, *J* = 13.5, 8.2 Hz, H8b), 0.78 - 1.20 (6H, m, H17 & 19)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 190.7 (C13), 162.6 (C15), 155.6 (C6), 137.9 (C9), 136.9 (C4), 136.6 (C21), 129.6 (C11), 128.4 (C22), 128.3 (C2), 128.1 (C23), 127.7 (C24), 127.6 (C10), 127.4 (C1), 127.1 (C12), 126.3 (C3), 93.7 (C14), 66.1 (C5), 60.4 (C7), 44. 0 (C16 & 18), 40.5 (C8), 11.2 (C17 & 19)

HRMS (ESI+): found $[M + Na]^+$ 479.2291, $C_{29}H_{32}N_2O_3Na^+$ required 479.2311.

5.5.2.3. Benzyl (S)-(2-phenyl-1-(3-phenyl-1H-pyrazol-5-yl)ethyl)carbamate (216)



A solution of benzyl (*S*)-(5-(diethylamino)-3-oxo-1,5-diphenylpent-4-en-2-yl)carbamate **215** (150 mg, 0.331 mmol, 1.0 eq.), hydrazine monohydrate (20.0 µL, 0.341 mmol, 1.1 eq.), and concentrated aqueous hydrochloric acid (37% w/w, 10.0 µL, 0.341 mmol, 1.1 eq.) in ethanol (1.5 mL, 0.16 M) was refluxed for 3 h. The reaction was cooled to room temperature and the solvent removed under reduced pressure. The resulting residue was diluted with water (10 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude compound was purified by flash column chromatography on silica eluting with 50% ethyl acetate in 40-60 petroleum ether to yield the title compound **216** as a white solid (108 mg, 0.272 mmol, 83%).

R_f = 0.27 (40% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -1.2 (c = 0.4 in $CHCl_3$)

IR: ν_{max} = 3304 (m, N-H), 3294 (m, N-H), 3032 (m, C-H), 1698 (s, C=O), 1539 (s, C=O), 1494 (s, N-H)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.62 (2H, d, *J* = 7.3 Hz, H3), 7.40 (2H, t, *J* = 7.3 Hz, H2), 7.27 - 7.36 (1H, m, H1), 7.19 - 7.26 (4H, m, H18 & 19), 7.18 - 7.26 (4H, m, H10, 12 & 20), 7.15 (2H, d, *J* =

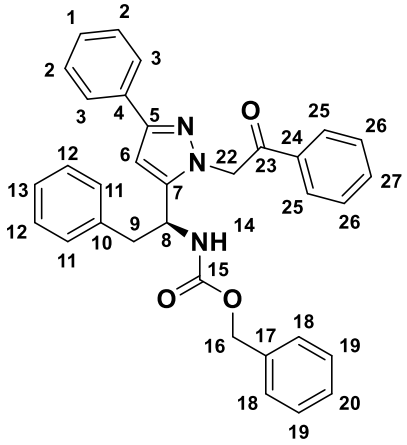
6.4 Hz, H11), 6.37 (1H, br s, H6), 5.53 - 5.65 (1H, br s, H14), 5.17 (1H, d, *J* = 6.7 Hz, H8), 5.11 (1H, d, *J* = 12.2 Hz, H16a), 5.05 (1H, d, *J* = 12.2 Hz, H16b), 3.23 (2H, s, H9)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 156.2 (C15), 150.3 (C7), 147.1 (C5), 136.9 (C10), 136.3 (C17), 131.2 (C4), 129.4 (C11), 128.9 (C2), 128.5, 128.4 (C12 & 19), 128.2 (C1), 128.1 (C18), 128.0 (C20), 126.8 (C13), 125.6 (C3), 100.8 (C6),. 66.9 (C16), 49.9 (C8), 43.1 (C9)

HRMS (ESI+): found $[M + H]^+$ 398.1877, $C_{25}H_{24}N_3O_2^+$ required 398.1869

This data is in accordance with that previously reported.[146]

5.5.2.4. Benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-pyrazol-5-yl)-2-phenylethyl)carbamate (217)



Following General Procedure 5: benzyl (*S*)-(2-phenyl-1-(3-phenyl-1*H*-pyrazol-5-yl)ethyl)carbamate **216** (87.0 mg, 0.220 mmol), 2-bromoacetophenone (52.0 mg, 0.260 mmol) and diisopropylethylamine (0.04 mL, 0.220 mmol) in THF (1 mL) were used. The crude product was purified by flash column chromatography eluting with 0-50% ethyl acetate in 40-60 petroleum ether to yield the title compound **217** as a dark yellow oil (31.0 mg, 0.060 mmol, 27%).

R_f = 0.68 (30% EtOAc in hexane)

$[\alpha]_D^{20}$ = +3.8 (c = 0.1 in CH_3OH)

IR: ν_{max} = 2917 (m, C-H), 1698 (s, C=O), 1597 (m, C=C)

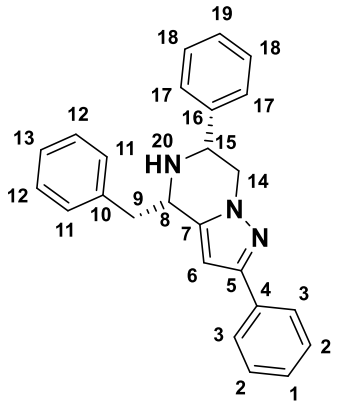
^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.93 - 8.02 (2H, m, H3), 7.80 (2H, d, *J* = 7.2 Hz, H25), 7.64 (1H, t, *J* = 7.4 Hz, H1), 7.52 (2H, t, *J* = 7.4 Hz, H2), 7.41 (2H, t, *J* = 7.2 Hz, H26), 7.20 - 7.36 (10H, m, H11,

12, 18, 19, 20 & 27), 7.12 - 7.15 (1H, m, H13), 6.63 (1H, s, H6), 5.75 (2H, m, H22), 4.97 - 5.06 (2H, m, H8 & 14), 4.86 (1H, d, *J* = 12.3 Hz, H16a), 4.70 (1H, d, *J* = 12.3 Hz, H16b), 3.41 (1H, dd, *J* = 12.3, 4.4 Hz, H9a), 3.10 - 3.23 (1H, m, H9b)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 191.9 (C23), 155.8 (C15), 151.2 (C7), 145.5 (C5), 136.6 (C10), 135.3 (C17), 134.5 (C24), 134.1 (C4), 134.0 (C1), 133.2 (C27), 129.3 (C12), 128.9 (C2), 128.7 (C19), 128.6 (C11), 128.5 (C26), 128.4, (C3), 128.1 (C13), 127.8 (C18), 126.9 (C20), 125.8 (C25), 101.6 (C6), 74.7 (C16), 57.7 (C22), 56.2 (C8), 41.0 (C9)

HRMS (ESI+): found $[M + H]^+$ 516.2267, $C_{33}H_{30}N_3O_3^+$ required 516.2287.

5.5.2.5. (4S,6R)-4-benzyl-2,6-diphenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (218)



Following General Procedure 6: benzyl (*S*)-(1-(1-(2-oxo-2-phenylethyl)-1*H*-pyrazol-5-yl)-2-phenylethyl)carbamate **217** (27.0 mg, 52.3 μmol), ammonium formate (99.0 mg, 1.57 mmol) and palladium dihydroxide (8.00 mg, 10.4 μmol) in ethyl acetate (1 mL) and methanol and water (1 mL, 3:1 v:v,) was used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in 40-60 petroleum ether to yield the title compound **218** as a pink solid (3.90 mg, 10.7 μmol, 20%).

R_f = 0.55 (30% EtOAc in hexane)

$[\alpha]_D^{20}$ = -20.9 (c = 0.1 in CH_3OH)

IR: ν_{max} = 2911 (m, C-H), 1633 (m, C=N), 1606 (m, C=C), 1550 (w, C=C), 1496 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 7.65 - 7.72 (4H, m, H3 & 17), 7.56 - 7.62 (3H, m, H1 & 2), 7.46 - 7.53 (4H, m, H11 & 18), 7.37 - 7.44 (3H, m, H12 & 19), 7.34 (1H, t, *J* = 7.6 Hz, H13), 6.35 (1H, s, H6), 5.32 (1H, dd, *J* = 8.2, 6.7 Hz, H8), 5.17 (1H, dd, *J* = 11.9, 4.6 Hz, H15), 4.77 (1H, dd, *J* = 13.4, 4.6 Hz,

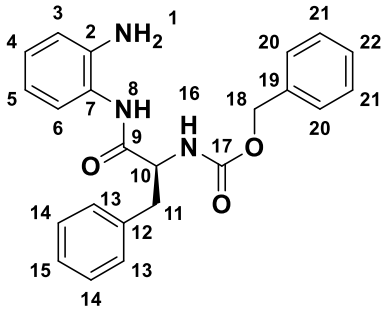
H14a), 4.68 (1H, dd, *J* = 13.4, 11.9 Hz, H14b), 3.54 (1H, dd, *J* = 14.3, 8.2 Hz, H9a), 3.47 (1H, dd, *J* = 14.3, 6.7 Hz, H9b)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 153.8 (C5), 138.1 (C7), 136.1 (C10), 133.9 (C4), 133.6 (C16), 131.8 (C1), 130.9 (C2), 130.7 (C18), 130.5 (C11), 129.9 (C12), 129.6 (C13), 129.3 (C19), 129.2 (C17), 126.7 (C3), 102.3 (C6), 59.8 (C15), 57.0 (C8), 51.2 (C14), 39.4 (C9)

HRMS (ESI+): found $[M + H]^+$ 366.1959, $C_{25}H_{24}N_4O_3^+$ required 366.1970.

5.6. Efficient Synthesis of Benzimidazole Heterocycles

5.6.1. Benzyl (1-((2-aminophenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (225)



A solution of Cbz-*L*-phenylalanine **49** (1.00 g, 3.34 mmol, 1.0 eq.), HATU (1.40 g, 3.67 mmol, 1.1 eq.) and diisopropylethylamine (3.00 mL, 16.7 mmol, 5.0 eq.) was stirred at room temperature for 5 minutes, before the addition of *o*-phenylenediamine **224** (542 mg, 5.01 mmol, 1.5 eq.). The reaction was then stirred at room temperature overnight. The reaction was diluted with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed with brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude compound was purified by flash column chromatography on silica eluting with 0-100% ethyl acetate in 40-60 petroleum ether to yield the title compound **225** as a yellow solid (1.19 g, 3.05 mmol, 91%).

R_f = 0.58 (50% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +6.3 (c = 0.4 in $CHCl_3$)

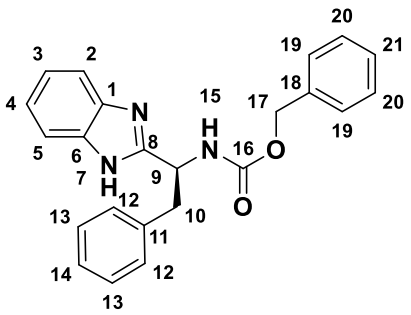
IR: ν_{max} = 3344 (m, N-H), 3304 (m, N-H), 1690 (s, C=O), 1648 (m, C=O), 1526 (s, N-H), 1453 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.47 (2H, br s, H1), 7.32 - 7.40 (7H, m, H13, 20, 21 & 22), 7.23 - 7.31 (3H, m, H14 & 15), 7.16 (1H, s, H8), 7.07 (1H, d, *J* = 7.6 Hz, H6), 7.03 (1H, td, *J* = 7.6, 1.1 Hz, H4), 6.75 (1H, td, *J* = 7.6, 1.1 Hz, H5), 6.72 (1H, dd, *J* = 7.6, 1.1 Hz, H3), 5.57 (1H, br s, H16), 5.11 (2H, s, H18), 4.57 (1H, q, *J* = 7.4 Hz, H10), 3.20 (1H, dd, *J* = 13.7, 7.4 Hz, H11a), 3.16 (1H, dd, *J* = 13.7, 7.4 Hz, H11b)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C =169.7 (C9), 156.2 (C17), 140.3 (C2), 136.3 (C12), 136.0 (C19), 129.4 (C14), 129.0 (C13), 128.6 (C21), 128.3 (C22), 128.1 (C20), 127.4 (C4), 126.4 (C15), 125.5 (C6), 123.1 (C7), 119.3 (C5), 117.5 (C3), 67.3 (C18), 57.1 (C10), 38.5 (C11)

HRMS (ESI+): found $[M + H]^+$ 390.1819, $C_{23}H_{24}N_3O_3^+$ required 390.1818.

5.6.2. Benzyl (1-(1H-benzo[d]imidazol-2-yl)-2-phenylethyl)carbamate (226)



A solution of benzyl (1-((2-aminophenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **225** (652 mg, 1.67 mmol, 1.0 eq.) was stirred in acetic acid (2 mL, 0.6 M) at 40 °C for 2 h. The reaction was neutralised with a saturated aqueous sodium carbonate solution and extracted with ethyl acetate (3 x 50 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude compound was purified by flash column chromatography on silica eluting with 0-30% ethyl acetate in 40-60 petroleum ether to yield the title compound **226** as an orange liquid (706 mg, 1.67 mmol, 100%).

R_f = 0.87 (30% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = -15.0 (c = 0.2 in $CHCl_3$)

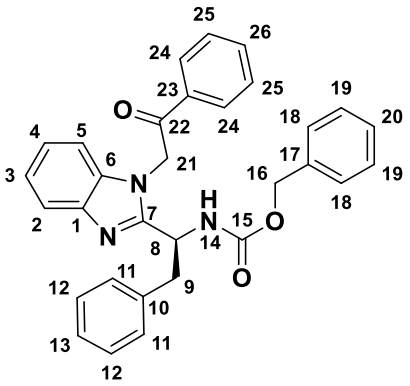
IR: ν_{max} = 3032 (m, N-H), 1694 (s, C=O), 1520 (s, N-H), 1496 (m, C=C), 1454 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.43 (2H, dd, *J* = 5.3, 2.9 Hz, H2 & 5), 7.29 - 7.36 (4H, m, H15, 20 & 21), 7.21 - 7.26 (4H, m, H3, 4 & 19), 7.15 - 7.20 (3H, m, H12 & 14), 7.07 - 7.13 (2H, m, H13), 5.30 (1H, q, *J* = 7.6 Hz, H9), 5.03 (1H, d, *J* = 12.5 Hz, H17a), 4.96 (1H, d, *J* = 12.5 Hz, H17b), 3.38 (2H, d, *J* = 7.6 Hz, H10)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 157.1 (C16), 154.0 (C8), 136.6 (C11), 136.4 (C1), 136.3 (C6), 136.1 (C18), 129.2 (C13), 128.6 (C12), 128.5 (C20), 128.1 (C21), 127.6 (C19), 126.9 (C14), 123.2, 123.3 (C3 & 4), 114.9 (br, C2 & 5), 67.0 (C17), 51.6 (C9), 40.2 (C10)

HRMS (ESI+): found $[M + H]^+$ 372.1718, $C_{23}H_{22}N_3O_2^+$ required 372.1712.

5.6.3. Benzyl (1-(1-(2-oxo-2-phenylethyl)-1H-benzo[d]imidazol-2-yl)-2-phenylethyl)carbamate (227)



Following general procedure 5: benzyl (1-(1*H*-benzo[d]imidazol-2-yl)-2-phenylethyl)carbamate **226** (400 mg, 1.07 mmol), 2-bromoacetophenone (257 mg, 1.29 mmol) and potassium carbonate (149 mg, 1.07 mmol) in acetone (4 mL) were used. The crude product was purified by flash column chromatography eluting with 0-50% ethyl acetate in 40-60 petroleum ether to yield the title compound **227** as a white solid (321 mg, 0.650 mmol, 61%).

R_f = 0.34 (30% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +23.8 (c = 0.2 in $CHCl_3$)

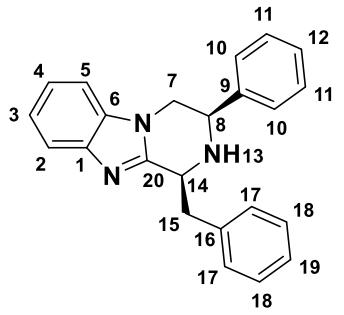
IR: ν_{max} = 3300 (m, N-H), 2928 (m, C-H), 1689 (s, C=O), 1523 (m, N-H), 1460 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.99 (2H, d, *J* = 7.6 Hz, H24), 7.82 (1H, d, *J* = 7.9 Hz, H2), 7.70 (1H, t, *J* = 7.6 Hz, H26), 7.56 (2H, t, *J* = 7.6 Hz, H25), 7.29 - 7.34 (4H, m, H3, 19 & 20), 7.27 (1H, d, *J* = 7.9 Hz, H4), 7.25 - 7.26 (1H, m, H13), 7.24 (2H, d, *J* = 2.4 Hz, H12), 7.18 (4H, d, *J* = 4.0 Hz, H11 & 18), 7.14 (1H, d, *J* = 7.9 Hz, H5), 5.76 (1H, d, *J* = 7.0 Hz, H14), 5.59 (1H, d, *J* = 18.3 Hz, H21a), 5.41 (1H, d, *J* = 18.3 Hz, H21b), 5.11 (1H, q, *J* = 7.0 Hz, H8), 4.95 (1H, d, *J* = 12.5 Hz, H16a), 4.81 (1H, d, *J* = 12.5 Hz, H16b), 3.50 (1H, dd, *J* = 13.7, 7.0 Hz, H9a), 3.46 (1H, dd, *J* = 13.7, 7.0 Hz, H9b)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 191.5 (C22), 155.9 (C15), 154.4 (C7), 142.2 (C1), 136.9 (C10), 136.1 (C23), 135.2 (C17), 134.3 (C26), 134.2 (C6), 129.4 (C11), 129.2 (C25), 129.0 (C12), 128.4 (C20), 128.1 (C24), 128.0 (C19), 127.6 (C18), 126.8 (C13), 123.1 (C3), 122.5 (C4), 119.8 (C2), 109.3 (C5), 66.8 (C16), 49.3, 49.2 (C8 & 21), 40.8 (C9)

HRMS (ESI+): found $[M + H]^+$ 490.2138, $C_{31}H_{28}N_3O_3^+$ required 490.2131.

5.6.4. (1S,3R)-1-benzyl-3-phenyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazine (228)



Following general procedure 6: benzyl (1-(1-(2-oxo-2-phenylethyl)-1*H*-benzo[d]imidazol-2-yl)-2-phenylethyl)carbamate **227** (90.0 mg, 0.180 mmol), ammonium formate (348 mg, 5.51 mmol) and palladium dihydroxide (26.0 mg, 36.7 μmol) in methanol and water (1 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with 0-40% ethyl acetate in 40-60 petroleum ether to yield the title compound **228** as a yellow solid (55.0 mg, 0.160 mmol, 89%).

R_f = 0.23 (20% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +3.0 (c = 0.1 in CH_3OH)

IR: ν_{max} = 2905 (m, C-H), 1694 (m, C=C), 1617 (m, C=C), 1536 (m, C=C)

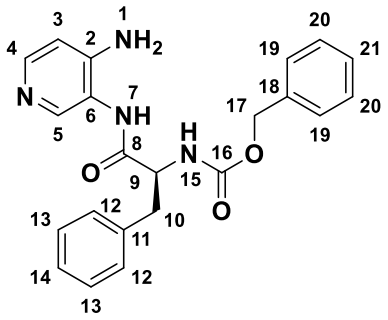
^{1}H NMR (500 MHz, CD_3OD): δ_H = 7.83 - 7.90 (2H, m, H2 & 5), 7.63 - 7.71 (4H, m, H3, 4 & 10), 7.43 - 7.51 (5H, m, H11, 12 & 17), 7.34 - 7.39 (2H, m, H18), 7.27 - 7.32 (1H, m, 19), 5.28 (1H, dd, *J* = 9.8, 3.7 Hz, H14), 4.83 (1H, dd, *J* = 11.7, 4.1 Hz, H8), 4.75 (1H, dd, *J* = 11.7, 4.1 Hz, H7a), 4.48 (1H, t, *J* = 11.7 Hz, H7b), 3.83 (1H, dd, *J* = 14.3, 3.7 Hz, H15a), 3.50 (1H, dd, *J* = 14.3, 9.8 Hz, H15b)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 149.9 (C20), 137.3 (C9), 136.1 (C16), 133.3, 133.2 (C1 & 6), 131.0 (C12), 130.7 (C17), 130.4 (C11), 130.2 (C19), 129.0 (C18), 128.9 (C10), 128.5, 127.6 (C3 & 4), 115.8 (C2), 113.7 (C5), 58.1 (C8), 56.3 (C14), 49.8 (C7), 38.77 (C15)

HRMS (ESI+): found $[M + H]^+$ 340.1817, $C_{23}H_{22}N_3^+$ required 340.1814.

5.7. Efficient Synthesis of Imidazopyridine Heterocycles

5.7.1. Benzyl (1-((4-aminopyridin-3-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (235)



A solution of Cbz-*L*-phenylalanine **49** (1.00 g, 3.34 mmol, 1.0 eq.), HATU (1.40 g, 3.67 mmol, 1.1. eq.) and diisopropylethylamine (3 mL, 16.7 mmol, 5.0 eq.) was stirred at room temperature for 5 minutes, before the addition of 3,4-diaminopyridine **234** (550 mg, 5.01 mmol, 1.5 eq.). The reaction was then stirred at room temperature overnight. The reaction was diluted with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed with brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude compound was purified by flash column chromatography on silica eluting with 0-30% methanol in diethyl ether to yield the title compound **235** as a yellow solid (931 mg, 2.39 mmol, 71%).

R_f = 0.41 (EtOAc)

$[\alpha]_D^{20}$ = +128.0 (c = 0.1 in $CHCl_3$)

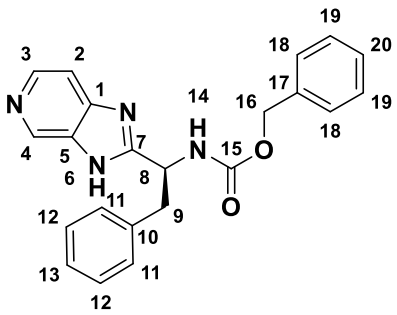
IR: ν_{max} = 3348 (m, N-H), 3175 (m, N-H), 1676 (s, C=O), 1586 (m, C=C), 1510 (s, N-H)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.06 (1H, s, H5), 7.96 (1H, d, *J* = 5.2 Hz, H4), 7.55 - 7.57 (1H, m, H3), 7.29 - 7.40 (9H, m, H12, 14, 19, 20, 21), 7.25 (2H, d, *J* = 7.3 Hz, H13), 5.57 (1H, br s H15), 5.13 (2H, s, H17), 4.58 (1H, dd, *J* = 7.2, 6.4 Hz, H9), 3.18 (2H, dd, *J*=7.2, 3.5 Hz, H10)

^{13}C NMR (126 MHz, $CDCl_3$): δ_c =169.9 (C8), 156.8, 152.3 (C2 & 16), 140.3 (C4), 136.0 (C5), 135.8 (C11), 129.3 (C13), 129.1, 128.8, 128.6 (C12, 20 & 21), 128.4 (C21), 128.0 (C19), 127.3 (C14), 116.6 (C6), 109.9 (C3), 67.5 (C17), 51.7 (C9), 39.2 (C10)

HRMS (ESI+): found $[M + H]^+$ 391.1775, $C_{22}H_{23}N_4O_3^+$ required 391.1770.

5.7.2. Benzyl (1-(3H-imidazo[4,5-c]pyridin-2-yl)-2-phenylethyl)carbamate (236)



A solution of benzyl (1-((4-aminopyridin-3-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate **235** (375 mg, 0.960 mmol, 1.0 eq.) was stirred in acetic acid (4 mL, 0.6 M) at 40 °C for 2h. The reaction was neutralised with a saturated aqueous sodium carbonate solution and extracted with ethyl acetate (3 x 25 mL). The combined organic fractions were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude compound was purified by flash column chromatography on silica eluting with 0-30% methanol in ethyl acetate to yield the title compound **236** as a clear liquid (292 mg, 0.780 mmol, 82%).

R_f = 0.64 (10% CH_3OH in EtOAc)

$[\alpha]_D^{20}$ = -35.8 (c = 0.5 in $CHCl_3$)

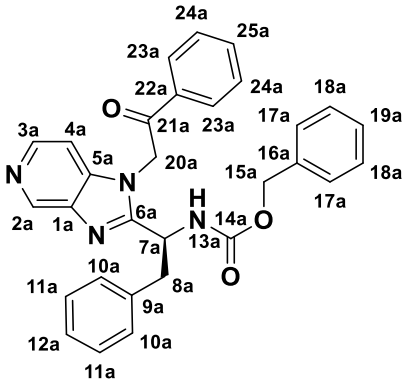
IR: ν_{max} = 3219 (m, N-H), 2882 (m, C-H), 1684 (s, C=O), 1621 (m, C=C), 1586 (m, C=C), 1560 (s, N-H)

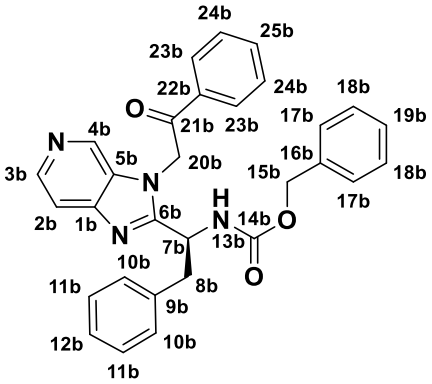
^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.91 (1H, s, H4), 8.31 (1H, d, *J* = 5.8 Hz, H3), 7.51 (1H, d, *J* = 5.8 Hz, H2), 7.27 - 7.30 (3H, m, H18 & 20), 7.21 - 7.26 (5H, m, H11, 13 & 19), 7.16 (2H, dd, *J* = 6.6, 2.9 Hz, H12), 6.05 (1H, d, *J* = 7.0 Hz, H14), 5.32 (1H, q, *J* = 7.0 Hz, H8), 5.06 (1H, d, *J* = 12.2 Hz, H16a), 5.01 (1H, d, *J* = 12.2 Hz, H16b), 3.38 - 3.54 (2H, m, H9)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 159.0 (C7), 156.7 (C15), 143.6 (C1), 139.1 (C3), 137.1 (C5), 136.9 (C4), 136.1 (C10), 135.8 (C17), 129.2 (C12), 128.8, 128.5 (C11 & 19), 128.3 (C20), 127.9 (C18), 127.2 (C13), 110.2 (C2), 67.3 (C16), 51.9 (C8), 39.5 (C9)

HRMS (ESI+): found $[M + H]^+$ 373.1671, $C_{22}H_{21}N_4O_2^+$ required 373.1665.

5.7.3. Benzyl (1-(1-(2-oxo-2-phenylethyl)-1H-imidazo[4,5-c]pyridin-2-yl)-2-phenylethyl)carbamate (237) and Benzyl (1-(3-(2-oxo-2-phenylethyl)-3H-imidazo[4,5-c]pyridin-2-yl)-2-phenylethyl)carbamate (238)





Following General Procedure 5: benzyl (1-(3*H*-imidazo[4,5-c]pyridin-2-yl)-2-phenylethyl)carbamate **236** (200 mg, 0.53 mmol), 2-bromoacetophenone **55** (128 mg, 0.64 mmol) and potassium carbonate (74 mg, 0.53 mmol) in acetone (2.5 mL) were used. The crude product was purified by flash column chromatography eluting with 0-30% methanol in ethyl acetate to yield the title compounds **237** & **238** as a yellow solid (79.6 mg, 0.16 mmol, 30%).

R_f = 0.61 & 0.68 (30% CH_3OH in EtOAc)

$[\alpha]_D^{20}$ = +37.3 (c = 0.3 in $CHCl_3$)

IR: ν_{max} = 3031 (m, N-H), 2928 (m, C-H), 1694 (s, C=O), 1610 (m, C=C), 1581 (m, C=C), 1527 (m, C=C), 1494 (m, C=C)

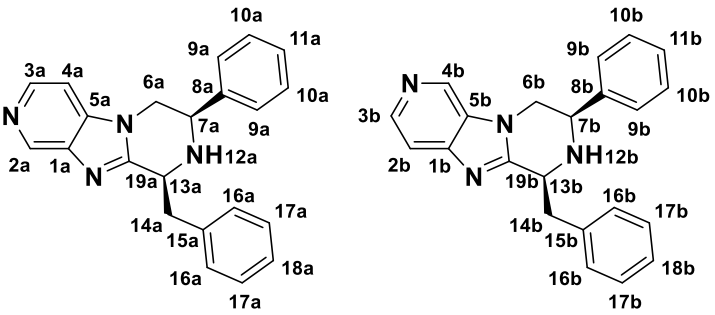
^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 9.14 (1H, s, H2a), 8.60 (1H, s, H4b), 8.50 (1H, d, *J* = 5.5 Hz, H2b), 8.43 (1H, d, *J* = 5.5 Hz, H4a), 7.99 (4H, d, *J* = 7.3 Hz, H23a & 23b), 7.72 - 7.74 (2H, m H25a & 25b), 7.71 (1H, dt, *J* = 2.7, 1.3 Hz, H3a), 7.58 (4H, td, *J* = 7.7, 3.5 Hz, H24a & 24b), 7.29 - 7.33 (6H, m, H17a, 17b 19a & 19b), 7.24 - 7.27 (6H, m, H12a, 12b, 18a & 18b), 7.14 - 7.21 (8H, m, H10a, 10b, 11a, 11b), 7.10 (1H, d, *J* = 5.5 Hz, H3b), 5.71 (2H, t, *J* = 4.3 Hz, H13a & 13b), 5.59 - 5.68 (2H, m, H20b), 5.48 (1H, d, *J* = 14.6 Hz, H20aa), 5.45 (1H, d, *J* = 15.0 Hz, H20ab), 5.11 (2H, dd, *J* = 18.0, 7.6 Hz, H7a & 7b), 4.91 - 4.99 (2H, m, H15b), 4.84 (1H, d, *J* = 12.5 Hz, H15aa), 4.79 (1H, d, *J* = 12.5 Hz, H15ab), 3.51 (1H, dd, *J* = 14.0, 6.7 Hz, H8aa), 3.41 - 3.48 (3H, m, H8b & 8ab)

^{13}C NMR (126 MHz, $CDCl_3$): δ_H = 190.9, 190.8 (C21a & 21b), 157.7 (C6b), 156.1 (C6a), 155.9, 155.9 (C14a & 14b), 147.4 (C1b), 142.7 (C2a), 142.5 (C4a), 142.4 (C2b), 140.4, (C1a), 139.5 (C5a), 136.5, 136.4 (C9a & 9b), 135.9, 135.9 (C16a & 16b), 134.6, 134.6 (C25a & 25b), 133.8, 133.8 (C22a & 22b),

133.0 (C5b), 132.9 (C4b), 129.4, 129.3 (C10a & 10b), 129.2, 129.2 (C24a & 24b), 128.7, 128.7 (C18a & 18b), 128.5, 128.5 (C17a & 17b), 128.2, 128.2 (C19a & 19b), 128.1, 128.1 (C23a & 23b), 127.7, 127.7 (C11a & 11b), 127.1, 127.0 (C12a & 12b), 114.5 (C3a), 105.0 (C3b), 67.0, 67.0 (C15a & 15b), 49.5, 49.4, 49.2 (C7a, 7b, 20a & 20b), 40.7, 40.6 (C8a & 8b)

HRMS (ESI+): found $[M + H]^+$ 491.2103, $C_{30}H_{27}N_4O_3^+$ required 491.2083.

5.7.4. (7R,9S)-9-benzyl-7-phenyl-6,7,8,9-tetrahydropyrido[3',4':4,5]imidazo[1,2-a]pyrazine (239) and (6S,8R)-6-benzyl-8-phenyl-6,7,8,9-tetrahydropyrido[4',3':4,5]imidazo[1,2-a]pyrazine (240)



Following General Procedure 6: benzyl (1-(1-(2-oxo-2-phenylethyl)-1*H*-imidazo[4,5-c]pyridin-2-yl)-2-phenylethyl)carbamate **237** and benzyl (1-(3-(2-oxo-2-phenylethyl)-3*H*-imidazo[4,5-c]pyridin-2-yl)-2-phenylethyl)carbamate **238** (44.0 mg, 89.7 μmol), ammonium formate (170 mg, 2.69 mmol) and palladium dihydroxide (13.0 mg, 17.9 μmol) in methanol and water (1 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with 0-40% ethyl acetate in 40-60 petroleum ether to yield the title compounds **239** & **240** as a yellow solid (30.0 mg, 89.3 μmol, 90%).

R_f = 0.22 & 0.28 (30% CH_3OH in EtOAc)

$[\alpha]_D^{20}$ = 0.0 (c = 0.2 in CH_3OH)

IR: ν_{max} = 2972 (m, C-H), 2900 (m, C-H), 1643 (m, C=N), 1615 (m, C=C), 1546 (m, C=C)

^{1}H NMR (500 MHz, CD_3OD): δ_H = 9.44 (2H, s, H2b & H4a), 8.61 - 8.69 (2H, m, H3a & 3b), 8.24 - 8.34 (2H, m, H2a & 4b), 7.83 (4H, dd, *J* = 7.5, 2.3 Hz, H9a & 9b), 7.51 - 7.61 (10H, m, H10a, 10b, 11a, 11b, 16a & 16b), 7.36 - 7.43 (4H, m, H17a & 17b), 7.29 - 7.34 (2H, m, H18a & 18b), 5.55 (2H, ddd, *J* = 14.3, 8.9, 5.2 Hz, H13a & 13b), 5.18 - 5.27 (2H, m, H7a & 7b), 4.99 - 5.10 (4H, m, H6a & 6b), 4.00 - 4.17 (2H, m, H14aa & 14ab), 3.69 (2H, ddd, *J* = 14.8, 8.9, 2.9 Hz, H14ab & 14bb)

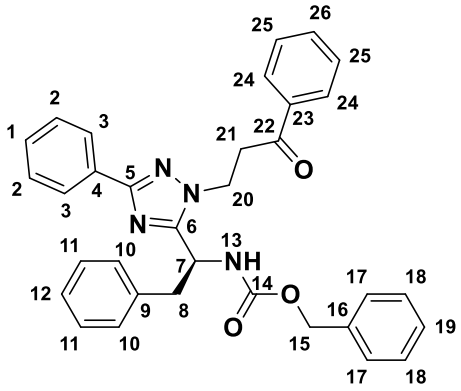
^{13}C NMR (126 MHz, CD_3OD): δ_C = 159.6, 156.4 (C19a & 19b), 154.3 (C1a), 145.9 (C1b), 141.4 (C5b), 136.5 (C2b), 136.2, 136.1 (C15a & 15b), 135.4, 135.3 (C3a & 3b), 134.0, 133.7 (C8a & 8b), 131.8 (C16a & 16b), 131.0, 130.8 (C10a, 10b, 11a &11b), 130.3, 130.2 (C17a & 17b), 129.9 (C9a & 9b), 129.7, 129.7 (C16a & 16b), 129.6 (C4a), 129.0, 129.0 (C18a & 18b), 118.5 (C2a), 110.8 (C4b), 59.3, 59.2 (C7a & 7b), 58.9, 58.8 (C13a & 13b), 48.0, 47.8 (C6a & 6b), 38.2, 38.1 (C14a & 14b)

HRMS (ESI+): found $[M + H]^+$ 341.1772, $C_{22}H_{21}N_4^+$ required 341.1766.

5.8. Efficient synthesis of 7- and 8-membered saturated rings.

5.8.1. Synthesis of the 7-membered ring.

5.8.1.1. Benzyl (S)-(1-(1-(3-oxo-3-phenylpropyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (245)



Following General Procedure 5: benzyl (1-(1*H*-indol-2-yl)-2-phenylethyl)carbamate **54** (100 mg, 0.25 mmol), 3-chloropropiophenone (46 mg, 0.28 mmol) and potassium carbonate (35 mg, 0.25 mmol) in acetone (1 mL), were used. The crude product was purified by flash column chromatography eluting with 20% ethyl acetate in 40-60 petroleum ether to yield the title compound **245** as a white solid (124 mg, 0.23 mmol, 93%).

R_f = 0.25 (20% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +13.5 (c = 0.3 in $CHCl_3$)

IR: ν_{max} = 3030 (m, C-H), 1697 (s, C=O), 1600 (m, C=C), 1524 (m, N-H)

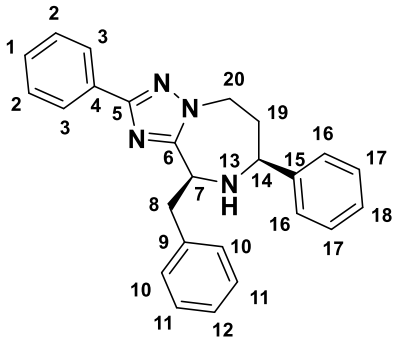
^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.07 (2H, dd, *J* = 8.0, 1.5 Hz, H3), 7.87 (2H, d, *J* = 7.5 Hz, H24), 7.59 (1H, tt, *J* = 7.2, 1.5 Hz, H1), 7.40 - 7.50 (5H, m, H2, 25 & 26), 7.30 - 7.39 (5H, m, H17, 18 & 19), 7.23 (2H, t, *J* = 7.5 Hz, H11), 7.16 (3H, d, *J* = 7.5 Hz, H10 & 12), 5.81 (1H, d, *J* = 8.6 Hz, H13), 5.34 (1H, td, *J* = 8.6, 6.3 Hz, H7), 5.16 (1H, d, *J* = 12.3 Hz, H15a), 5.10 (1H, d, *J* = 12.3 Hz, H15b), 4.23 (2H, t, *J* = 6.8 Hz, H20), 3.36 - 3.51 (2H, m, H8a & H21a), 3.25 (1H, dd, *J* = 12.9, 8.6 Hz, H8b), 2.89 (1H, dt, *J* = 18.1, 7.0 Hz, H21b)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C =196.7 (C22), 161.4 (C5), 155.8 (C6), 155.6 (C14), 136.4 (C9), 136.2 (C16), 136.1 (C23), 133.4 (C26), 130.9 (C4), 129.5 (C11), 129.2 (C10), 128.7 (C25), 128.6, 128.5,

128.5 (C2, 18 & 19), 128.2 (C1), 128.1, 128.0 (C17 & 24), 127.1 (C12), 126.3 (C3), 67.0 (C15), 48.8 (C7), 43.0 (C20), 41.7 (C8), 37.9 (C21)

HRMS (ESI+): found $[M + H]^+$ 531.2395, $C_{33}H_{31}N_4O_3^+$ required 531.2396.

5.8.1.2. (7S,9S)-9-benzyl-2,7-diphenyl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[1,5-a][1,4]diazepine (246)



Following the protocol for the ring closure, benzyl (*S*)-(1-(1-(2-oxo-2-phenylethyl)-5-phenyl-1*H*-imidazol-2-yl)-2-phenylethyl)carbamate **245** (75.0 mg, 141 μmol), ammonium formate (267 mg, 4.24 mmol) and palladium dihydroxide (19.8 mg, 28.3 μmol) in methanol and water (1 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with 30% ethyl acetate in 40-60 petroleum ether to yield the title compound **246** as a white solid (10.6 mg, 27.9 μmol, 20%).

R_f = 0.78 (30% EtOAc in hexane)

$[\alpha]_D^{20}$ = +103.1 (c = 0.1 in CH_3OH)

IR: ν_{max} = 2925 (m, C-H), 1684 (m, C=N), 1604 (m, C=C), 1482 (m, C=C)

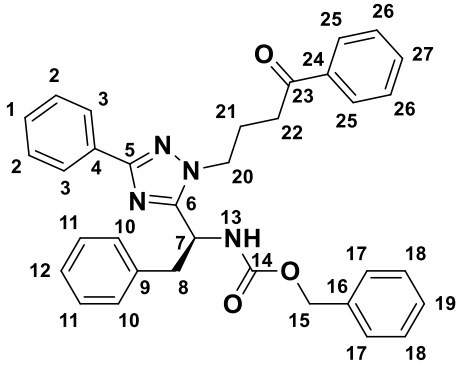
^{1}H NMR (400 MHz, CD_3OD): δ_H = 8.08 (2H, dd, *J* = 7.9 H3), 7.65 (2H, d, *J* = 7.6 Hz, H16), 7.41 - 7.58 (8H, m, H1, 2, 10, 17 & 18), 7.34 (2H, t, *J* = 7.3 Hz, H11), 7.25 (1H, d, *J* = 7.3 Hz, H12), 5.27 (1H, dd, *J* = 10.5, 1.9 Hz, H7), 5.07 (1H, d, *J* = 11.4, 3.4 Hz, H14), 4.80 (1H, dd, *J* = 13.4, 3.4 Hz, H20a), 4.68 (1H, dd, *J* = 13.4, 11.4, H20b), 3.98 (1H, dd, *J* = 13.0, 10.5 Hz, H8a), 3.57 (1H, dd, *J* = 13.0, 1.9 Hz, H8b), 2.33 - 2.50 (2H, m, H19)

^{13}C NMR (101 MHz, CD_3OD): δ_C = 161.9 (C5), 152.6 (C6), 138.7 (C15), 137.1 (C9), 132.0 (C4), 131.3 (C10), 131.2 (C1), 130.8 (C17), 130.7 (C2), 129.9 (C18), 129.6 (C11), 128.6 (C16), 128.4 (C12), 127.4 (C3), 68.0 (C14), 57.5 (C7), 37.0 (C8), 34.4 (C20) – C19 obscured by CD_3OD peak

HRMS (ESI+): found $[M + H]^+$ 381.2079, $C_{25}H_{25}N_4^+$ required 381.2079.

5.8.2. Attempted synthesis of the 8-membered ring

5.8.2.1. Benzyl (S)-(1-(1-(4-oxo-4-phenylbutyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (249)



A stirred solution of 4-chlorobutyrophenone **247** (0.501 mL, 3.11 mmol, 1.0 eq.), triethyl orthoformate (0.780 mL, 4.67 mmol, 1.5 eq.), trifluoromethane sulfonic acid (0.030 mL, 0.31 mmol, 0.1 eq.) and ethylene glycol (0.260 mL, 4.67 mmol, 1.5 eq.) in toluene (2 mL) was heated to reflux for 12 hours. Upon complete consumption of starting material, as detected using TLC (10% ethyl acetate in 40-60 petroleum ether) the reaction was quenched with water (20 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic fractions were washed with brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude compound was distilled under vacuum to yield 2-(3-chloropropyl)-2-phenyl-1,3-dioxolane **251** (470 mg, 2.08 mmol, 67%).

Following General Procedure 5: benzyl (1-(1*H*-indol-2-yl)-2-phenylethyl)carbamate **54** (100 mg, 0.251 mmol), 2-(3-chloropropyl)-2-phenyl-1,3-dioxolane **251** (57.2 mg, 0.252 mmol) and triethylamine (38.5 μL, 0.276 mmol) in acetonitrile (1 mL) were used. The crude product was purified by flash column chromatography eluting with 30% EtOAc in 40-60 petroleum ether. The protected ketone was dissolved in dichloromethane and washed with an aqueous solution of 1 M hydrochloric acid, dried ($MgSO_4$) and concentrated under reduced pressure to yield the title compound **249** as a white solid (77.4 mg, 0.142 mmol, 56%).

R_f = 0.52 (30% EtOAc in 40-60 petroleum ether)

$[\alpha]_D^{20}$ = +17.0 (c = 0.5 in CH_3OH)

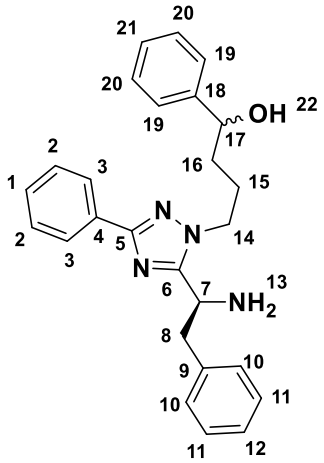
IR: ν_{max} = 3271 (m, N-H), 2929 (m, N-H), 1674 (s, C=O), 1629 (s, C=O), 1520 (m, C=C), 1503 (m, C=C)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.05 (2H, dt, *J* = 6.7, 1.5 Hz, H3), 7.91 (2H, d, *J* = 7.6 Hz, H25), 7.56 (1H, t, *J* = 7.3 Hz, H27), 7.39 - 7.48 (5H, m, H1, 2 & 26), 7.30 - 7.38 (5H, m, H17, 18 & 19), 7.20 (2H, t, *J* = 7.3 Hz, H11), 7.15 (1H, t, *J* = 7.3 Hz, H12), 7.10 (2H, d, *J* = 7.3 Hz, H10), 5.76 (1H, d, *J* = 8.5 Hz, H13), 5.18 (1H, ddd, *J* = 9.8, 8.5, 5.8 Hz, H7), 5.14 (1H, d, *J* = 12.5 Hz, H15a), 5.05 (1H, d, *J* = 12.5 Hz, H15b), 3.92 (1H, quin, *J* = 7.0 Hz, H20a), 3.85 (1H, quin, *J* = 7.0 Hz, H20b), 3.37 (1H, dd, *J* = 12.8, 5.8 Hz, H8a), 3.28 (1H, dd, *J* = 12.8, 9.8 Hz, H8b), 2.88 (1H, dt, *J* = 17.7, 7.0 Hz, H22a), 2.78 (1H, dt, *J* = 17.7, 7.0 Hz, H22b), 1.92 - 2.04 (2H, m, H21)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 198.7 (C23), 161.1 (C5), 155.6 (C6), 155.5 (C14), 136.7 (C24), 136.1 (C16), 133.0 (C27), 131.1 (C9), 131.0 (C4), 129.4 (C10), 129.1 (C1), 128.7 (C11), 128.6 (C17), 128.5 (C26), 128.5 (C2), 128.5 (C18), 128.2 (C19), 128.0 (C25), 127.1 (C12), 126.3 (C3), 67.0 (C15), 48.8 (C7), 47.0 (C20), 41.7 (C8), 34.8 (C22), 23.8 (C21)

HRMS (ESI+): found $[M + H]^+$ 545.2643, $C_{34}H_{33}N_4O_3^+$ required 545.2553.

5.8.2.2. (S)-4-(5-((S)-1-amino-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-1-yl)-1-phenylbutan-1-ol (253)



Following General Procedure 6: benzyl (*S*)-(1-(1-(2-oxo-2-phenylethyl)-5-phenyl-1*H*-imidazol-2-yl)-2-phenylethyl)carbamate **249** (38.1 mg, 70.0 μmol), ammonium formate (132 mg, 2.09 mmol) and palladium dihydroxide (10.0 mg, 14.0 μmol) in methanol and water (1 mL, 3:1 v:v,) was used. The crude product was purified by flash column chromatography eluting with ethyl acetate to yield the title compound **253** as a white solid (12.8 mg, 31.1 μmol, 44%).

R_f = 0.13 (EtOAc)

$[\alpha]_D^{20}$ = +116.7 (c = 0.2 in CH_3OH)

IR: ν_{max} = 2926 (m, C-H), 2878 (m, C-H), 1600 (m, C=C), 1485 (m, C=C)

^{1}H NMR (400 MHz, CD_3OD): δ_H = 8.07 (2H, dd, *J* = 7.7, 1.7 Hz, H3), 7.39 - 7.49 (3H, m, H1 & 2), 7.16 - 7.37 (8H, m, H11, 12, 19, 20 & 21), 7.02 - 7.10 (2H, m, H10), 4.91 (1H, dd, *J* = 10.2, 5.3 Hz, H7), 4.52 (1H, dd, *J* = 7.3, 5.4 Hz, H17), 3.64 - 3.74 (1H, m, H14a), 3.52 - 3.63 (1H, m, H14b), 3.40 (1H, dd, *J* = 13.1, 5.3 Hz, H8a), 3.25 - 3.27 (1H, m, H8b), 1.37 - 1.61 (4H, m, H15 & 16)

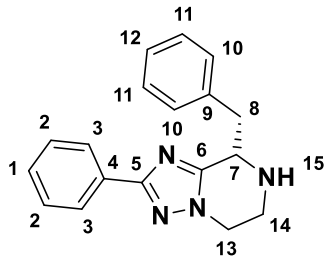
^{13}C NMR (126 MHz, CD_3OD): δ_C = 163.0 (C5), 153.3 (C6), 146.3 (C18), 135.6 (C9), 132.1 (C4), 130.8 (C10), 130.8 (C1), 130.3 (C20), 129.8 (C2), 129.5 (C11), 129.3 (C12), 128.5 (C21), 127.4 (C3), 127.1 (C19), 74.6 (C17), 41.0 (C8), 36.9 (C16), 27.2 (C15) – C7 and 14 obscured by solvent peak

HRMS (ESI+): found $[M + H]^+$ 413.2355, $C_{26}H_{29}N_4O^+$ required 413.2341.

5.9. Efficient Synthesis of Scaffolds with a Single Chiral Centre

5.9.1. Single Substiution in the R_2 position

5.9.1.1. (S)-8-benzyl-2-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (172)



Following General Procedure 6: benzyl 8-benzyl-6-hydroxy-2-phenyl-5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazine-7(8*H*)-carboxylate **175** (38.0 mg mg, 86.3 μmol), ammonium formate (163 mg, 2.59 mmol) and palladium (12.1 mg, 17.3 μmol) in methanol and water (1 mL, 3:1 v:v) was used. The crude product was purified by flash column chromatography eluting with ethyl acetate to yield the title compound **172** as a yellow solid (19.5 mg, 67.2 μmol, 78%).

R_f = 0.31 (60% EtOAc in hexane)

$[\alpha]_D^{20}$ = -97.2 (c = 0.1 in CH_3OH)

IR: ν_{max} = 2922 (m, C-H), 2850 (m, C-H), 1633 (w, C=C), 1491 (m, C=C)

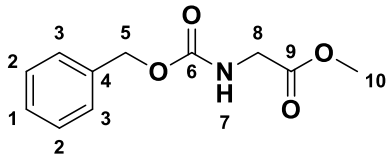
^{1}H NMR (500 MHz, CD_3OD): δ_H = 8.10 (2H, m, H3), 7.45 - 7.52 (7H, m, H1, 2, 10 & 11), 7.42 (1H, *J* = 3.5, 2.9 Hz, H12), 5.16 (1H, dd, *J* = 10.2, 4.3 Hz, H7), 4.62 (1H, ddd, *J* = 13.7, 5.1, 2.4 Hz, H13a), 4.53 (1H, ddd, *J* = 13.7, 10.9, 5.2 Hz, H13b), 3.97 (1H, dd, *J* = 15.1, 4.3 Hz, H8a), 3.90 (1H, ddd, *J* = 13.4, 5.2, 2.4 Hz, H14a), 3.76 (1H, ddd, *J* = 13.6, 10.9, 5.1 Hz, H14b), 3.25 (1 H, dd, *J* = 15.1, 10.2 Hz, H8b)

^{13}C NMR (126 MHz, CD_3OD): δ_C = 164.0 (C6), 151.2 (C5), 135.5 (C9), 131.8 (C4), 131.3 (C1), 131.0 (C2), 130.8 (C11), 130.1 (C10), 129.6 (C12), 127.7 (C3), 57.0 (C7), 44.9 (C13), 42.6 (C14), 38.2 (C8)

HRMS (ESI+): found $[M + H]^+$ 291.1622, $C_{18}H_{19}N_4$ required 291.1610.

5.9.2. Single Substiution in the R_3 position

5.9.2.1. Methyl ((benzyloxy)carbonyl)glycinate (259)



Following General Procedure 2: Cbz-*L*-glycine **258** (15.0 g, 71.7 mmol), thionyl chloride (7.30 mL, 100 mmol) and methanol (350 mL) were used. The crude product was purified by flash column chromatography eluting with 50% ethyl acetate in 40-60 petroleum ether to yield the title compound **259** as a cloudy white oil (15.4 g, 68.9 mmol, 96%).

R_f = 0.17 (50% EtOAc in 40-60 petroleum ether)

IR: ν_{max} = 3351 (m, C-N), 2954 (m, C-H), 1704 (s, C=O), 1520 (s, N-H)

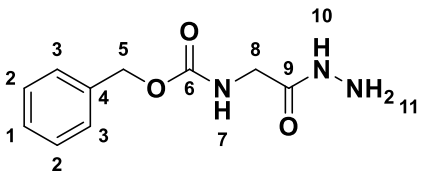
^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.28 - 7.40 (5H, m, H1, 2 & 3), 5.31 (1H, br s, H7.), 5.13 (2H, s, H5), 3.99 (2H, d, *J* = 5.5 Hz, H8), 3.75 (3H, s, H10)

^{13}C NMR (500 MHz, $CDCl_3$): δ_c = 170.4 (C9), 156.2 (C6), 136.2 (C4), 128.5 (C2), 128.2 (C1), 128.1 (C3), 67.1 (C5), 52.3 (C10), 42.6 (C8)

HRMS (ESI+): found $[M + Na]^+$ 246.0741, $C_{11}H_{13}NO_4Na^+$ required 246.0737

This data is in accordance with that previsouly recorded.[307]

5.9.2.2. Benzyl (2-hydrazinyl-2-oxoethyl)carbamate (260)



Following General Procedure 3: methyl ((benzyloxy)carbonyl)glycinate **259** (15.0 g, 67.2 mmol) and hydrazine monohydrate (16.0 mL, 336 mmol) in methanol (130 mL) were used to yield the title compound **260** as a white solid (14.8 g, 66.3 mmol, 98%).

R_f = 0.42 (EtOAc)

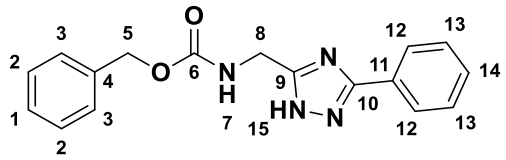
IR: ν_{max} = 3302 (s, N-H), 3034 (m, C-H), 1726 (s, C=O), 1651 (s, C=O), 1604 (m, C=C), 1528 (s, N-H)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.29 - 7.43 (5H, m, H1, 2 & 3), 5.41 (1H, br s, H7), 5.14 (2H, s, H5), 3.87 (3H, app. d, *J* = 6.1 Hz, H8 & 10), 1.63 (2H, br s, H11)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 169.7 (C9), 156.6 (C6), 135.9 (C4), 128.6 (C2), 128.4 (C1), 128.2 (C3), 67.4 (C5), 43.4 (C8)

HRMS (ESI+): found $[M + H]^+$ 224.1030, $C_{10}H_{14}N_3O_3^+$ required 224.1030.

5.9.2.3. Benzyl ((3-phenyl-1H-1,2,4-triazol-5-yl)methyl)carbamate (261)



Following General Procedure 4: ethyl benzimidate **53** (4.01 g, 26.9 mmol) and benzyl (2-hydrazinyl-2-oxoethyl)carbamate **260** (5.00 g, 22.4 mmol) in ethanol (45 mL), followed by acetic acid (22.5 mL) were used. The crude product was purified by flash column chromatography eluting with 0-100% ethyl acetate in 40-60 petroleum ether to yield the title compound **261** as a white solid (4.32 g, 14.0 mmol, 63%).

R_f = 0.33 (50% EtOAc in 40-60 petroleum ether)

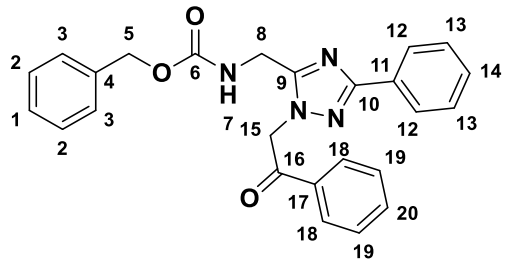
IR: ν_{max} = 3318 (m, N-H), 3126 (m, N-H), 2917 (m, C-H), 1682 (s, C=O), 1537 (s, N-H)

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.02 (2H, d, *J* = 7.2 Hz, H12), 7.45 - 7.58 (3H, m, H13 & 14), 7.30 - 7.42 (5H, m, H1, 2 & 3), 5.81 (1H, br s, H7), 5.18 (2H, s, H5), 4.71 (2H, d, *J* = 5.8 Hz, H8)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 165.3 (C10), 163.5 (C9), 156.1 (C6), 135.9 (C4), 131.8 (C14), 129.0 (C13), 128.5 (C2), 128.2 (C3), 128.1 (C1), 126.9 (C12), 123.4 (C11), 67.3 (C5), 36.2 (C8)

HRMS (ESI+): found $[M + H]^+$ 309.1356, $C_{17}H_{17}N_4O_2^+$ required 309.1352.

5.9.2.4. Benzyl ((1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)methyl)carbamate (262)



Following General Procedure 5: benzyl ((3-phenyl-1*H*-1,2,4-triazol-5-yl)methyl)carbamate **261** (4.00 mg, 13.0 mmol), 2-bromoacetophenone (3.10 mg, 15.6 mmol) and potassium carbonate (1.79 mg, 13.0 mmol) in acetone (10 mL) were used. The crude product was purified by flash column chromatography eluting with 0-60% ethyl acetate in 40-60 petroleum ether to yield the title compound **262** as a pale yellow solid (3.99 mg, 9.33 mmol, 72%).

R_f = 0.47 (40% EtOAc in 40-60 petroleum ether)

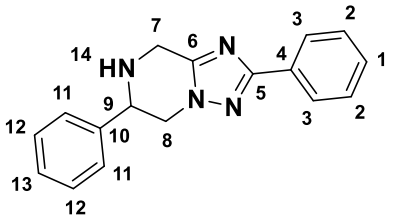
IR: ν_{max} = 3209 (m, N-H), 2936 (m, C-H), 1771 (m, C=O), 1711 (s, C=O), 1539 (m, N-H)

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.08 (2H, dd, *J* = 8.1, 1.4 Hz, H12), 8.03 (2H, d, *J* = 7.6 Hz, H18), 7.70 (1H, t, *J* = 7.6 Hz, H20), 7.57 (2H, t, *J* = 7.9 Hz, H19), 7.39 - 7.48 (3H, m, H13 & 14), 7.31 - 7.37 (3H, m, H1 & 2), 7.30 (2H, m, H3), 5.92 (2H, s, H15), 5.71 (1H, br s, H7), 5.00 (2H, s, H5), 4.54 (2H, d, *J* = 6.1 Hz, H8)

^{13}C NMR (126 MHz, $CDCl_3$): δ_C = 191.1 (C16), 161.1 (C10), 156.5 (C6), 154.6 (C9), 135.9 (C4), 134.4 (C20), 134.0 (C17), 130.3 (C11), 129.4 (C14), 129.1 (C19), 128.6 (C13), 128.6 (C2), 128.5 (C3), 128.2 (C18), 128.0 (C1), 126.3 (C12), 67.2 (C5), 55.1 (C15), 36.2 (C8)

HRMS (ESI+): found $[M + H]^+$ 427.1752, $C_{25}H_{23}N_4O_3^+$ required 427.1770.

5.9.2.5. 2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (263)



Following General Procedure 6: benzyl ((1-(2-oxo-2-phenylethyl)-3-phenyl-1*H*-1,2,4-triazol-5-yl)methyl)carbamate **262** (50.0 mg, 117 μmol), ammonium formate (15.0 mg, 234 mmol) and palladium dihydroxide (16.0 mg, 23.4 μmol) in methanol and water (1 mL, 3:1 v:v,) were used. The crude product was purified by flash column chromatography eluting with 0-100% ethyl acetate in 40-60 petroleum ether to yield the title compound **263** as a white solid (23.0 mg, 95.9 μmol, 82%).

R_f = 0.50 (60% EtOAc in 40-60 petroleum ether)

IR: ν_{max} = 2962 (m, C-H), 2938 (m, C-H), 1709 (s, C=N), 1701 (s, C=N)

^{1}H NMR (400 MHz, CD_3OD): δ_H = 8.00 - 8.17 (2H, m, H3), 7.67 - 7.73 (2H, m, H11), 7.58 - 7.64 (3H, m, H12 & 13), 7.46 - 7.52 (3H, m, H1 & 2), 5.25 (1H, dd, *J* = 11.2, 4.8 Hz, H9), 4.74 - 4.89 (4H, m, H7 & 8)

^{13}C NMR (101 MHz, CD_3OD): δ_C = 163.6 (C5), 147.5 (C6), 133.1 (C10), 131.8 (C13), 131.2 (C4), 131.0 (C1), 130.9 (C12), 129.8 (C2), 128.9 (C11), 127.3 (C3), 58.5 (C9), 58.5 (C8), 42.5 (C7)

HRMS (ESI+): found $[M + H]^+$ 277.1439, $C_{17}H_{17}N_4^+$ required 277.1448.

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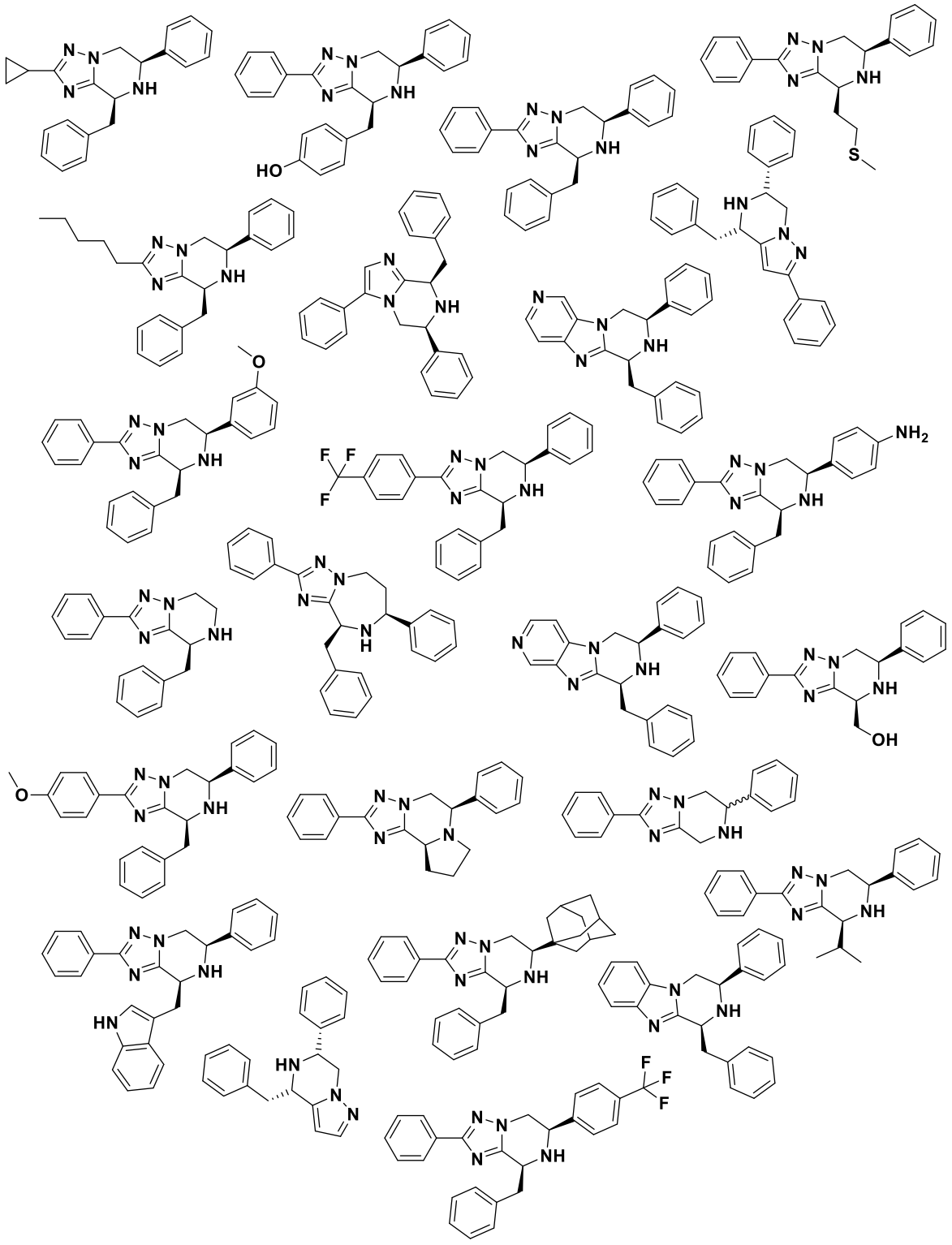
7. Appendix

7.1. Computational Procedures

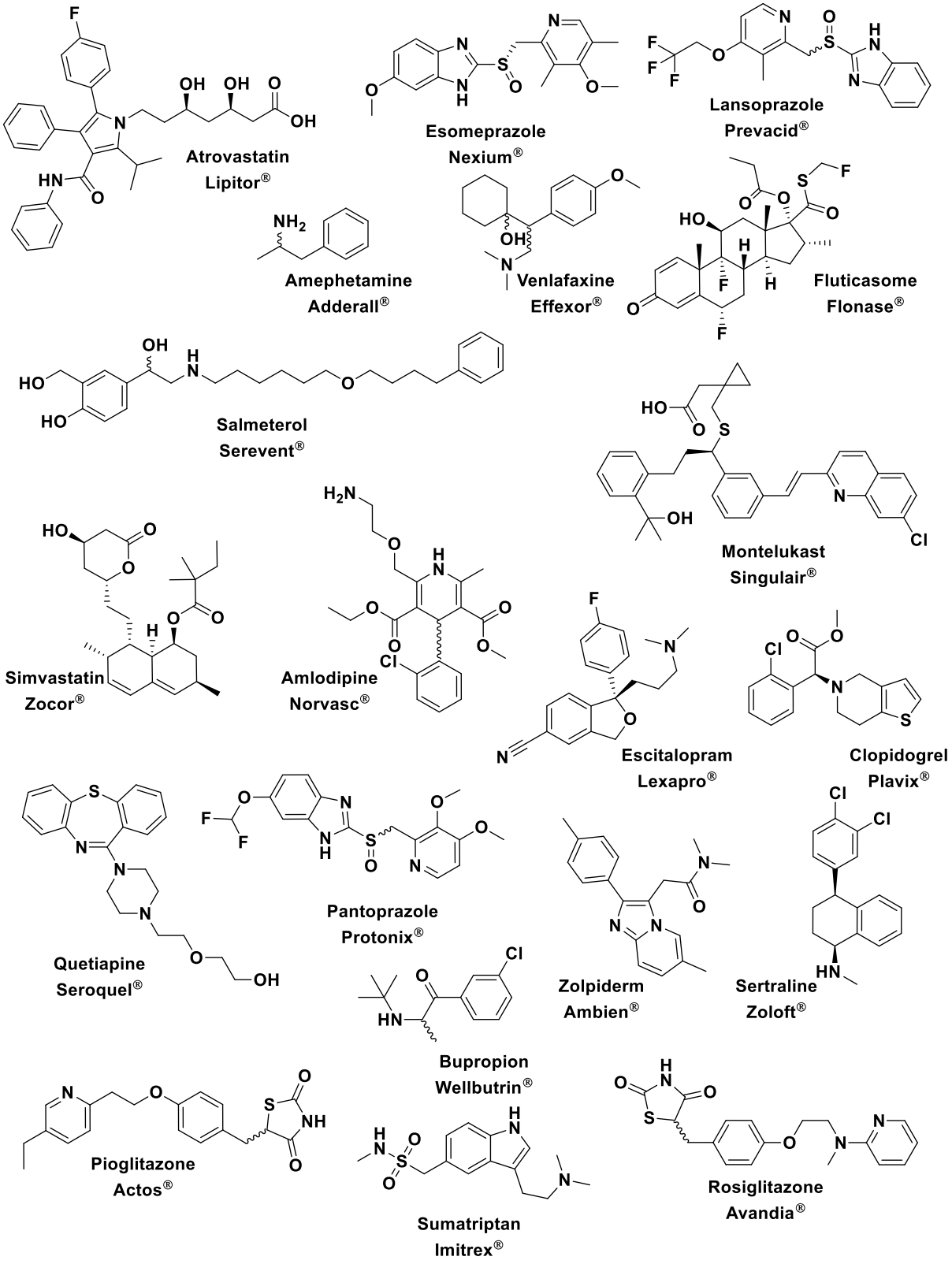
7.1.1. *Reference sets*

Collection 1: Our Library

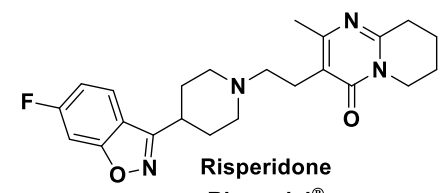


Collection 2: 40 high-profile synthetic drugs currently produced by the pharmaceutical industry

See: F. Kopp, C. F Stratton, L. B. Akella and D. S. Tan, *Nat. Chem. Biol.*, **2012**, *8*, 358.[308]



Collection 2: 40 high-profile synthetic drugs currently produced by the pharmaceutical industry (cont.)



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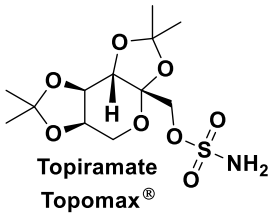
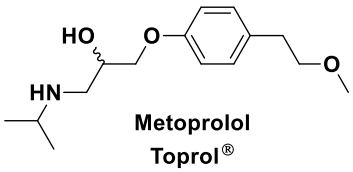
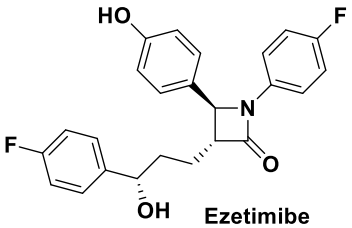
Risperdal®



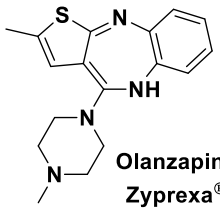
Topiramate
Topomax®



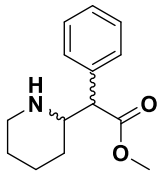
Metoprolol
Toprol®



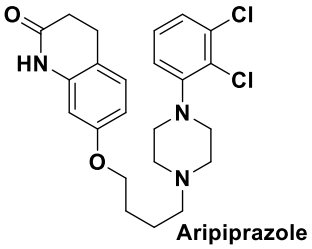
Ezetimibe
Zetia®



Olanzapine
Zyprexa®



Methylphenidate
Concerta®



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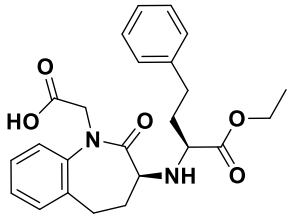
Abilify®



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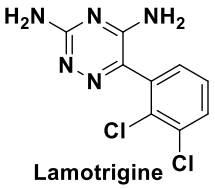
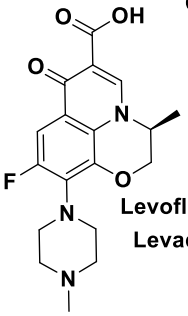
Lotensin®



Lamotrigine
Lamictal®



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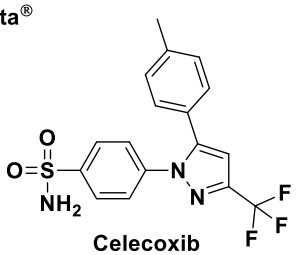
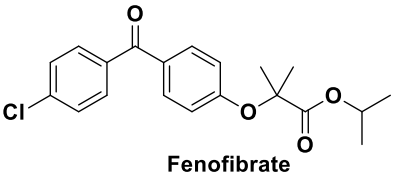
Levaquin®

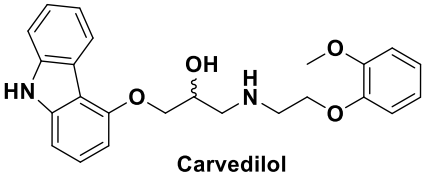


Celecoxib
Celebrex®

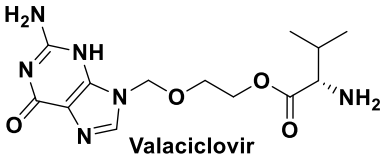
Alendronif Acid
Fosamax®



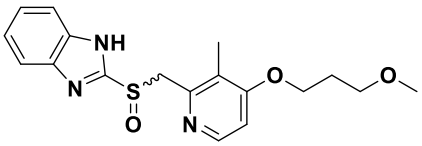
Fenofibrate
Tricor®



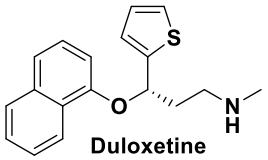
Carvedilol
Coreg®



Valaciclovir
Valtrex®



Rabeprazole
Aciphex®



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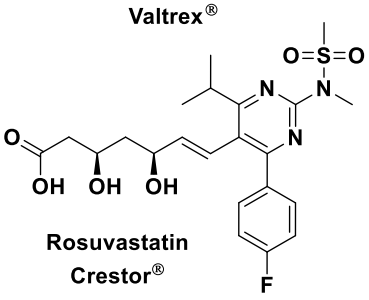
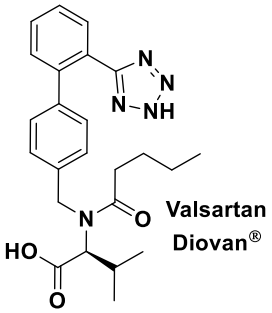
Cymbalta®



Rosuvastatin
Crestor®



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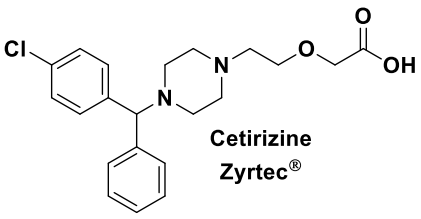
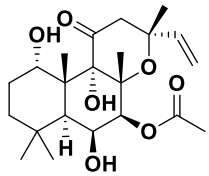
Diovan®



Cetirizine
Zyrtec®

Collection 3: 60 randomly selected natural products

See: F. Kopp, C. F Stratton, L. B. Akella and D. S. Tan, *Nat. Chem. Biol.*, **2012**, *8*, 358.[309]



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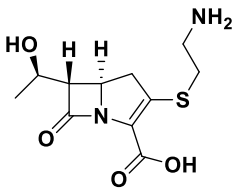

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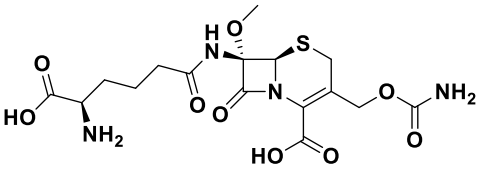

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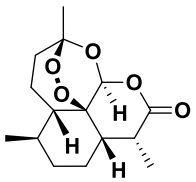

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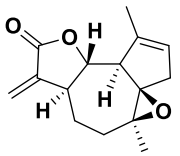

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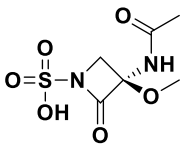

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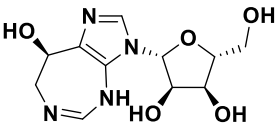

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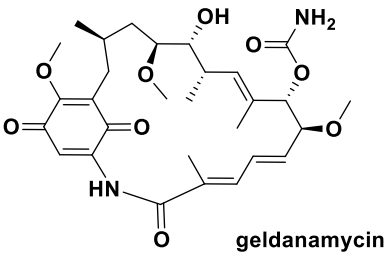

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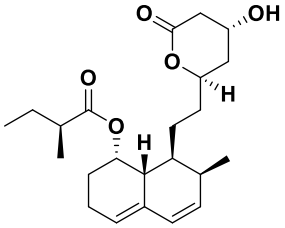

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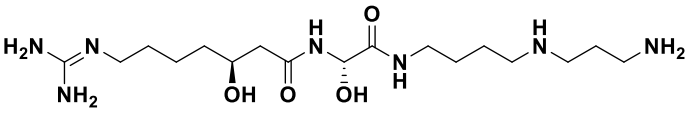

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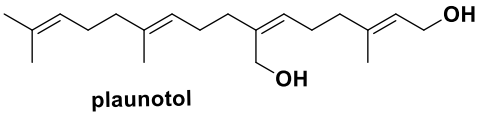

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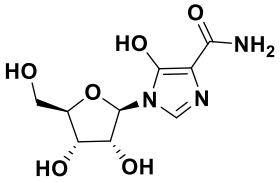

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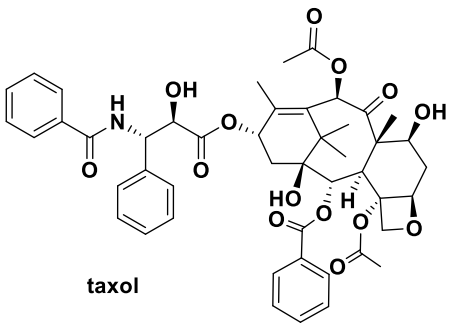
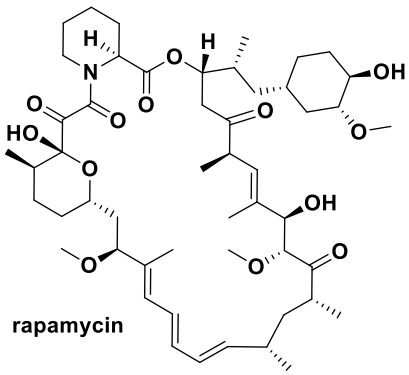
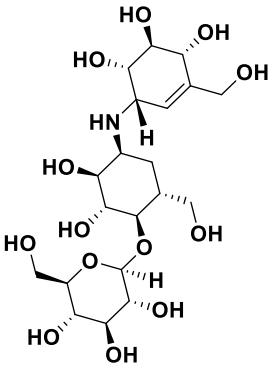


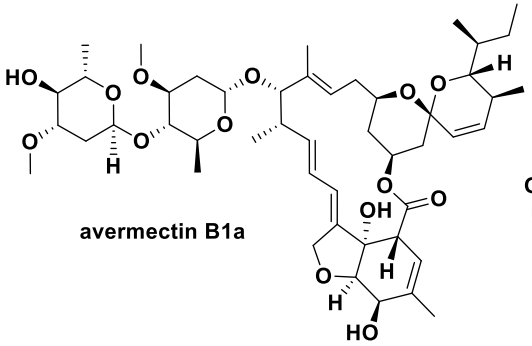
taxol



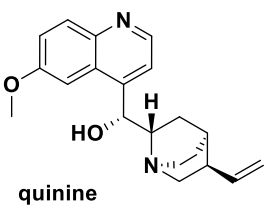
rapamycin



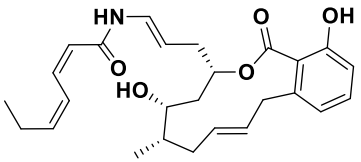
validamycin



avermectin B1a

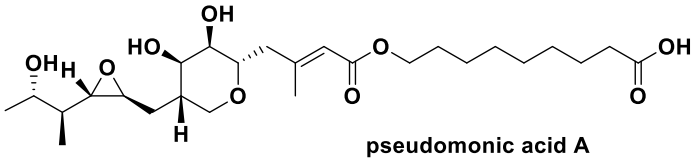


quinine

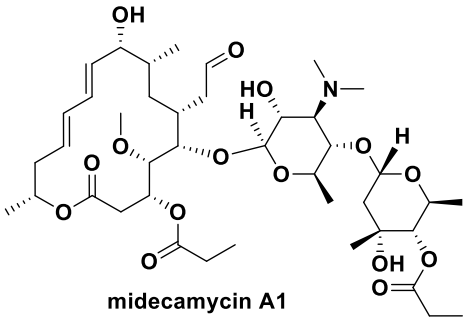


salicylihalamide A

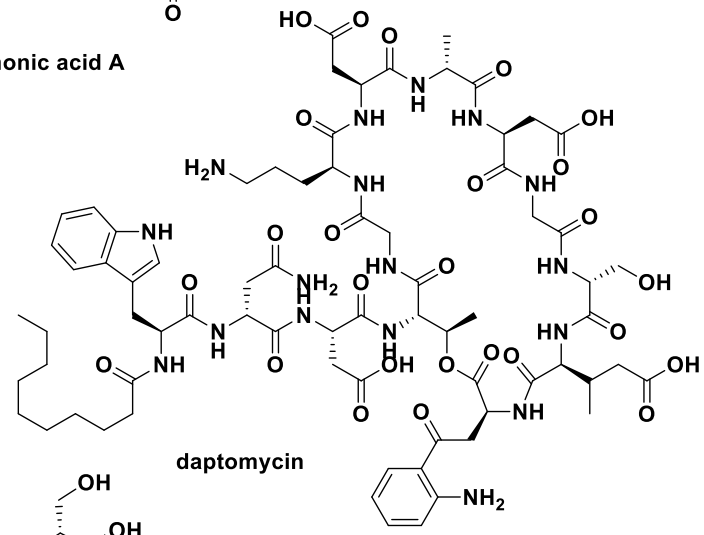
Collection 3: 60 randomly selected natural products (cont.)



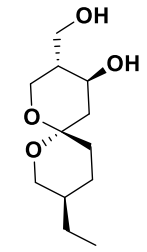
pseudomonic acid A



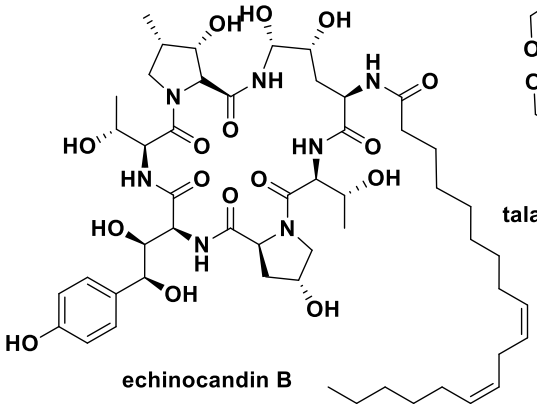
midecamycin A1



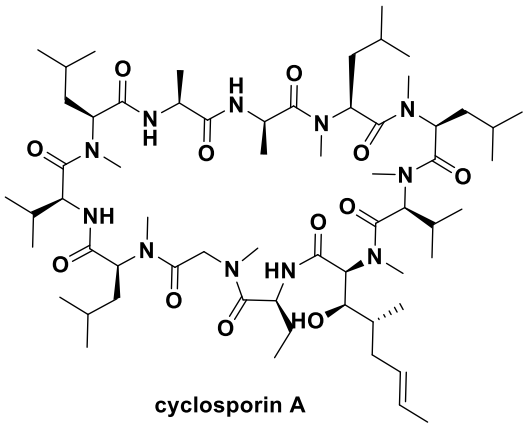
daptomycin



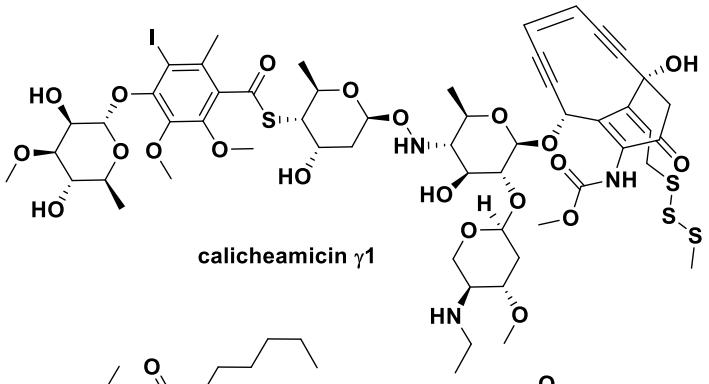
talaromycin B



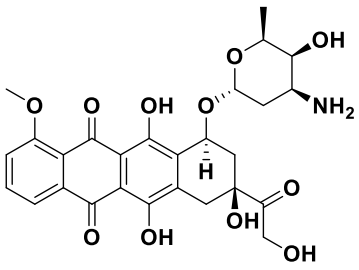
echinocandin B



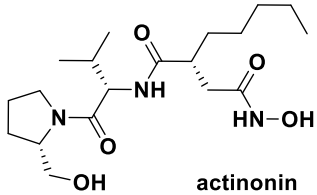
cyclosporin A



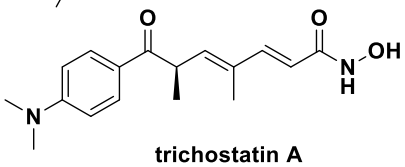
calicheamicin γ1



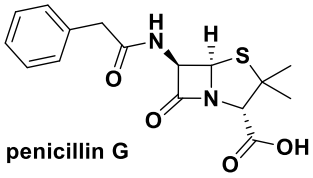
adriamycin



actinonin

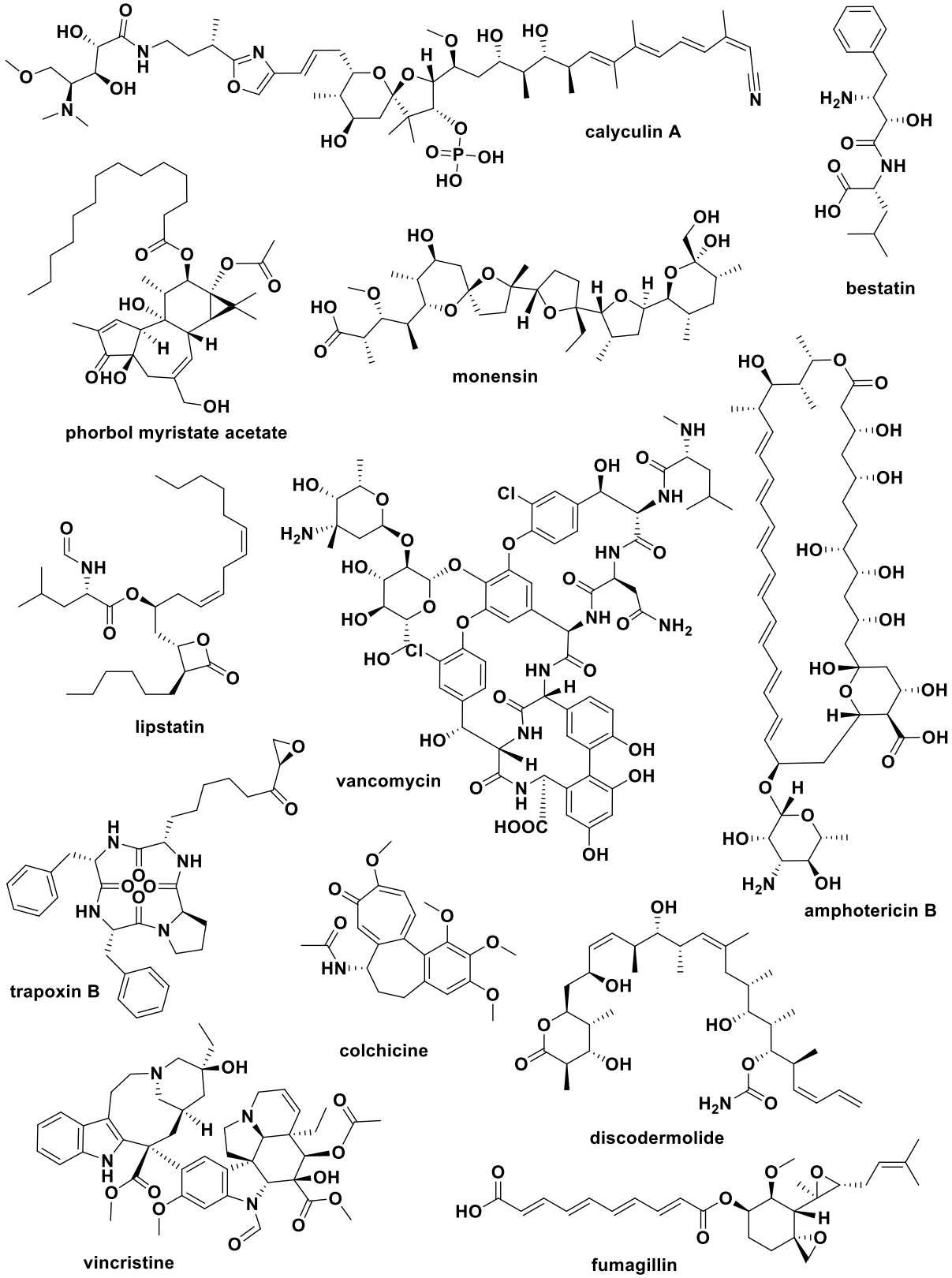


trichostatin A

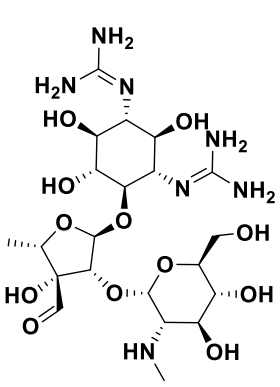


penicillin G

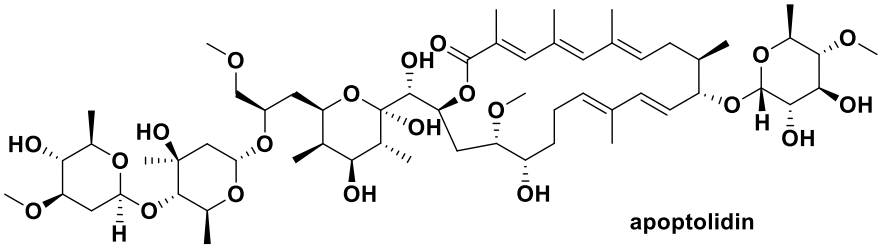
Collection 3: 60 randomly selected natural products (cont.)



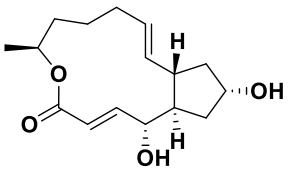
Collection 3: 60 randomly selected natural products (cont.)



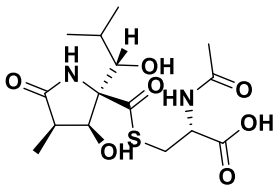
streptomycin



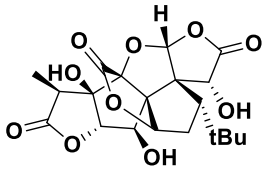
apoptolidin



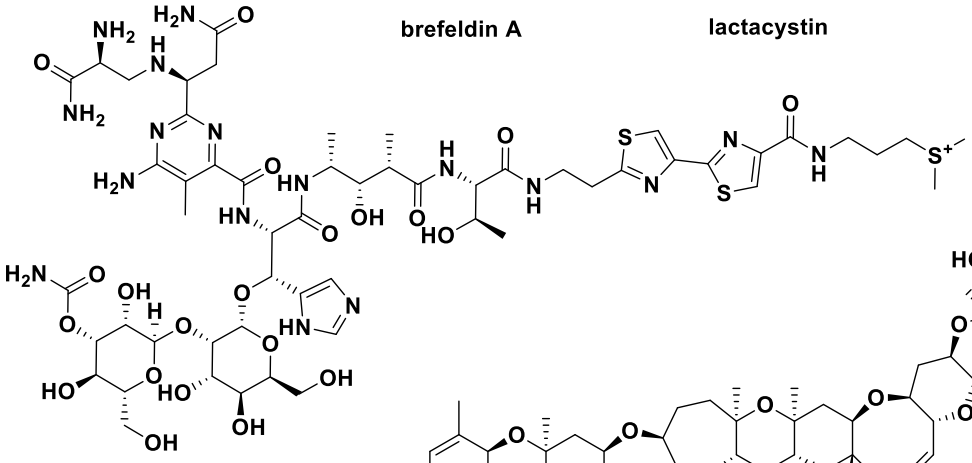
brefeldin A



lactacystin

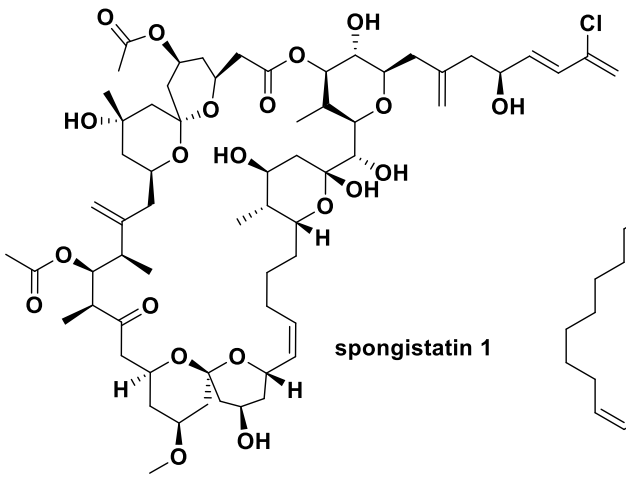


ginkgolide B

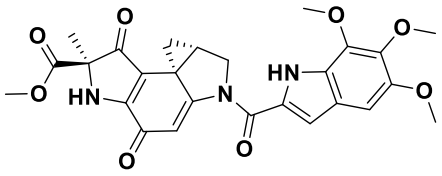


bleomycin A2

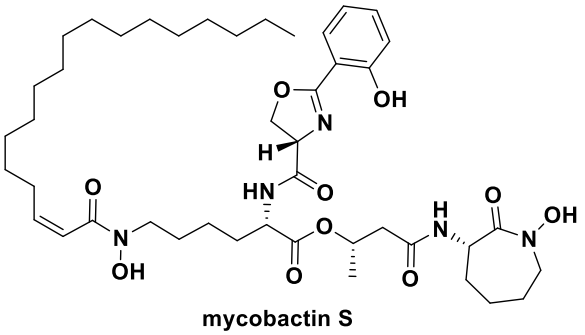
brevetoxin B



spongistatin 1

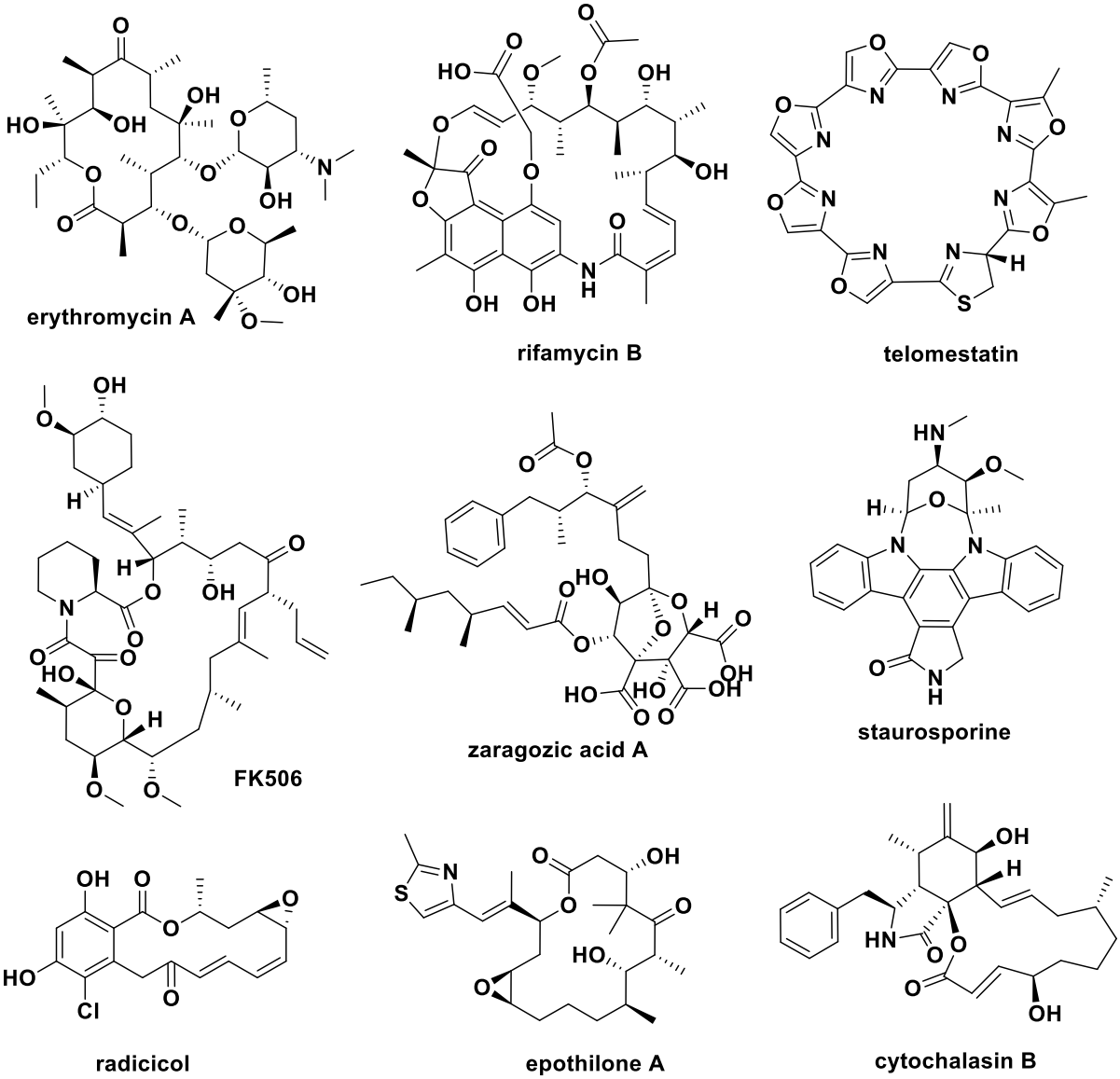


duocarmycin A



mycobactin S

Collection 3: 60 randomly selected natural products (cont.)



Collection 3: 1,000 Maybridge Fragment Library compounds.

See: N. Mateu, S. L. Kidd, L. Kalash, H. Sore, A. Madin, A. Bender and D. R. Spring, Chem. Eur. J. Accepted.[310]

This library is based on the core 1000-member collection within the Maybridge Fragment library. Details of the library (including SMILES and SDF) are available from 'http://www.maybridge.com/' under the 'Ro3 Fragment library section. More details can be found at: 'http://www.maybridge.com/images/pdfs/MB_Ro3_fragment_flyer_2011_EUR_v7.pdf'

7.1.2. Principle Moments of Inertia

Principal Moment of Inertia (PMI) was performed using Molecular Operating Environment (MOE) software package version 2012.10 from the Chemical Computing Group. Merck molecular force field 94X (MMFF94x), an all-atom force field parameterised for small organic molecules with the Generalised Born solvation model, was used to minimise the energy potential of the library members. A LowModeMD search was employed for the conformation generation. Detailed settings for conformational search are listed below (Table 7.1).

Only the conformer with the lowest energy was retained for principal moment of inertia (PMI) calculations. Normalized PMI ratios (I1/I3 and I2/I3) of these conformers were obtained from MOE and then plotted on a triangular graph, with the coordinates (0,1), (0.5,0.5) and (1,1) representing a perfect rod, disc and sphere respectively.

Table 7.1: Conformation search settings

Method	LowModeMD
Rejection Limit	100
RMS Gradient	0.005
Iteration Limit	10000
MM Iteration Limit	500
RMSD Limit	0.15
Energy Window	7
Conformation Limit	100

7.1.3. Prinical Component Analysis (PCA)

The library was merged with two reference sets and 17 molecular descriptors were calculated (Table 7.2)

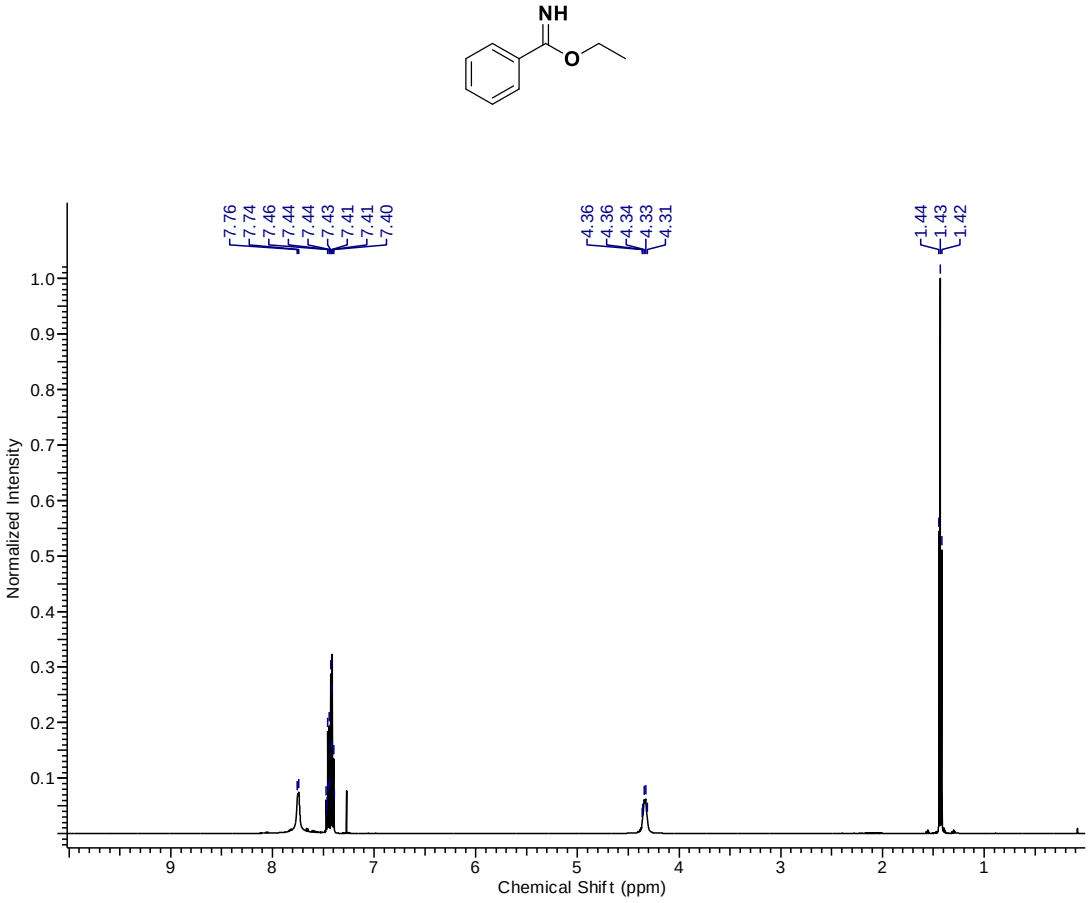
Table 7.2: 17 Descriptors selected for PCA

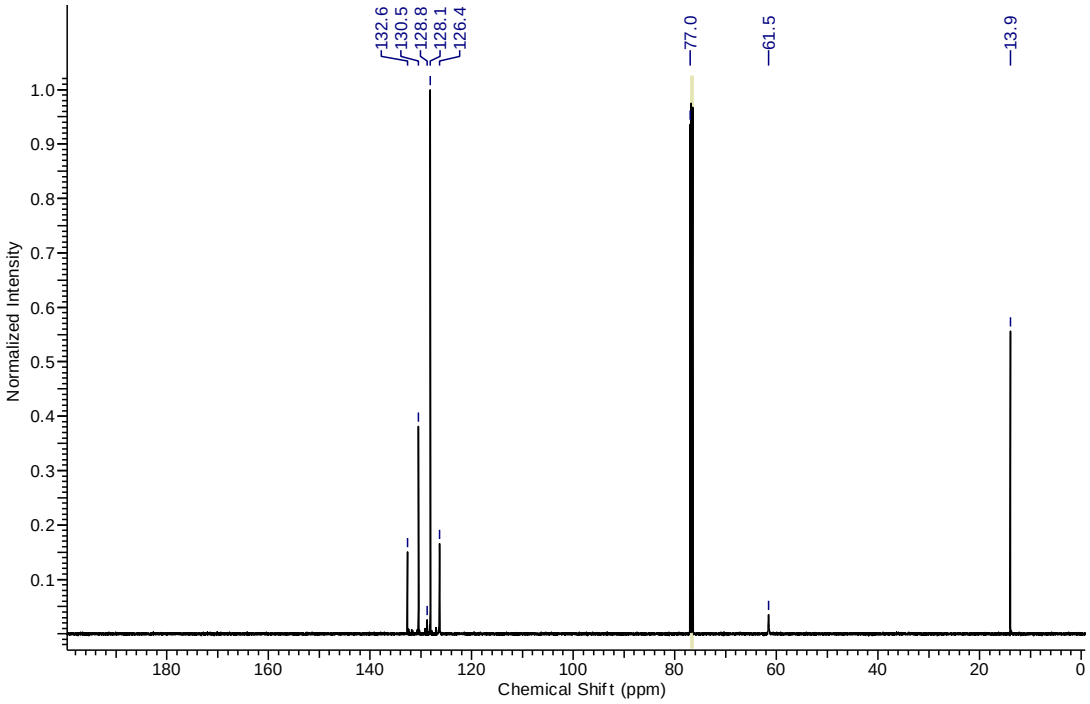
Desription	Parameter
Total hydrophobic surface area	ASA_H
Total polar surface area	ASA_P
Molecular flexibility	KierFlex
Log octanol/ water partition coefficient	SlogP
Topological polar surface area (Å^2)	TPSA
Molecular weight	Weight
Number of H-bond acceptor atoms	a_acc
Number of aromatic atoms	a_aro
Number of H-bond donor atoms	a_don
Number of Nitrogen atoms	a_nN
Number of Oxygen atoms	a_nO
Number of rotatable bonds	b_rotN
Number of chiral centres	chiral
Partiton coefficient	logS
Molar refractivity	mr
Number of rings	rings
Van der Waals volume	vol

7.2. Spectra

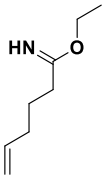
7.2.1. Efficient Synthesis of cis-1,2,4-Triazole Heterocycle

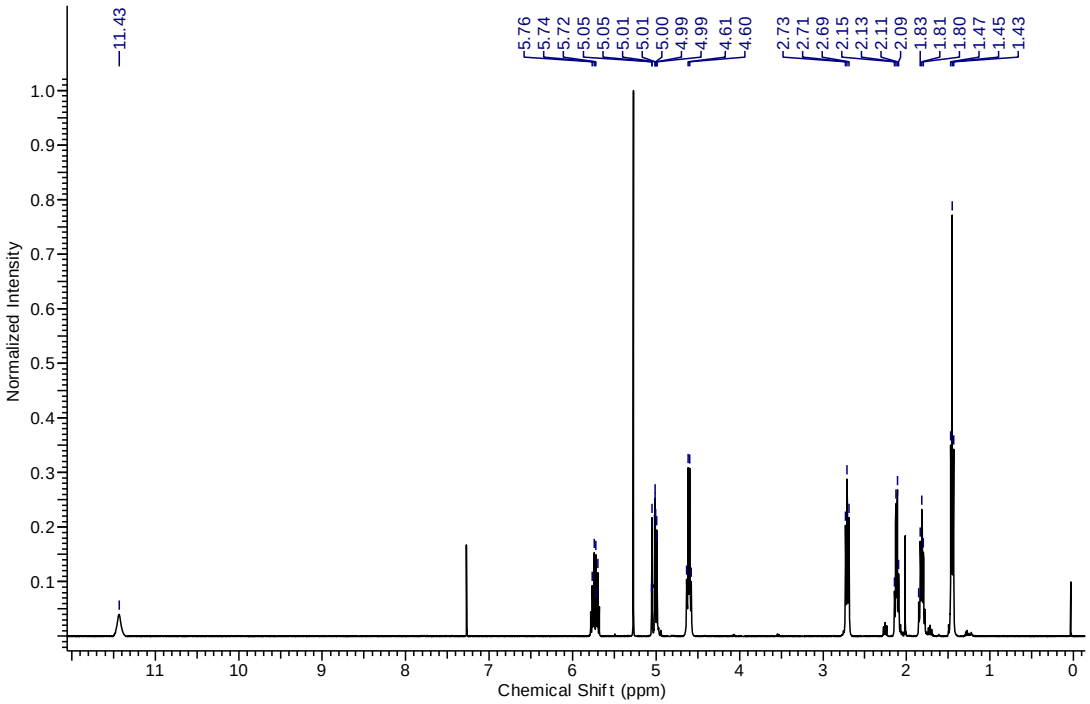
Ethyl benzimidate (53)

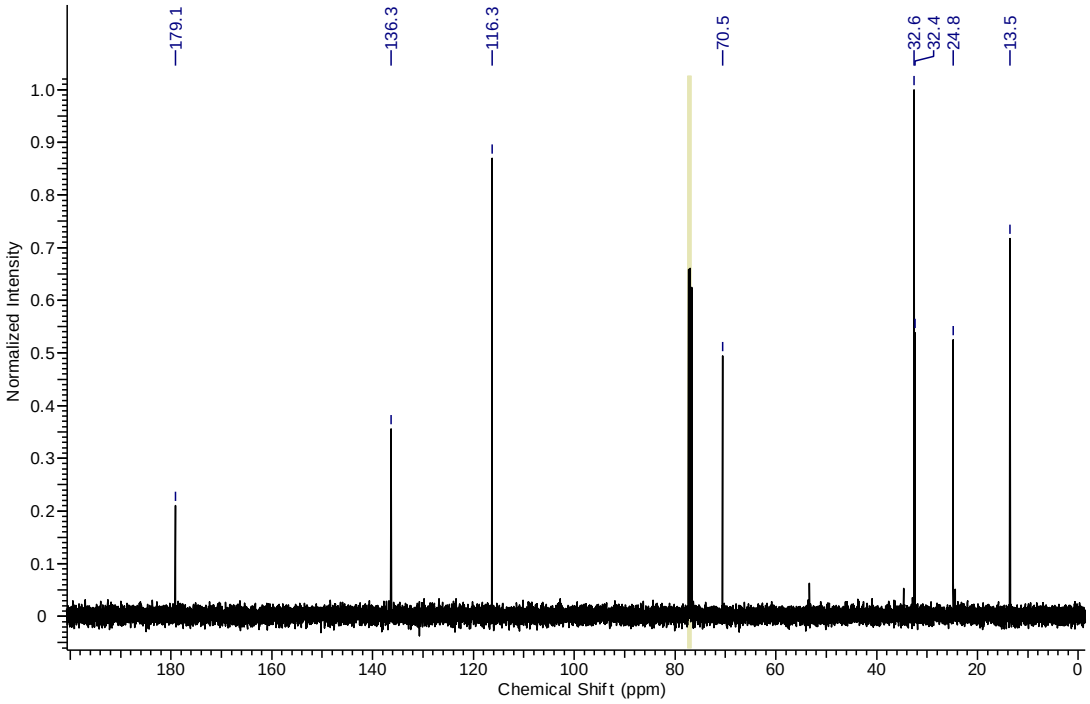




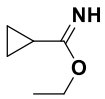
Ethyl hex-5-enimidate (77)

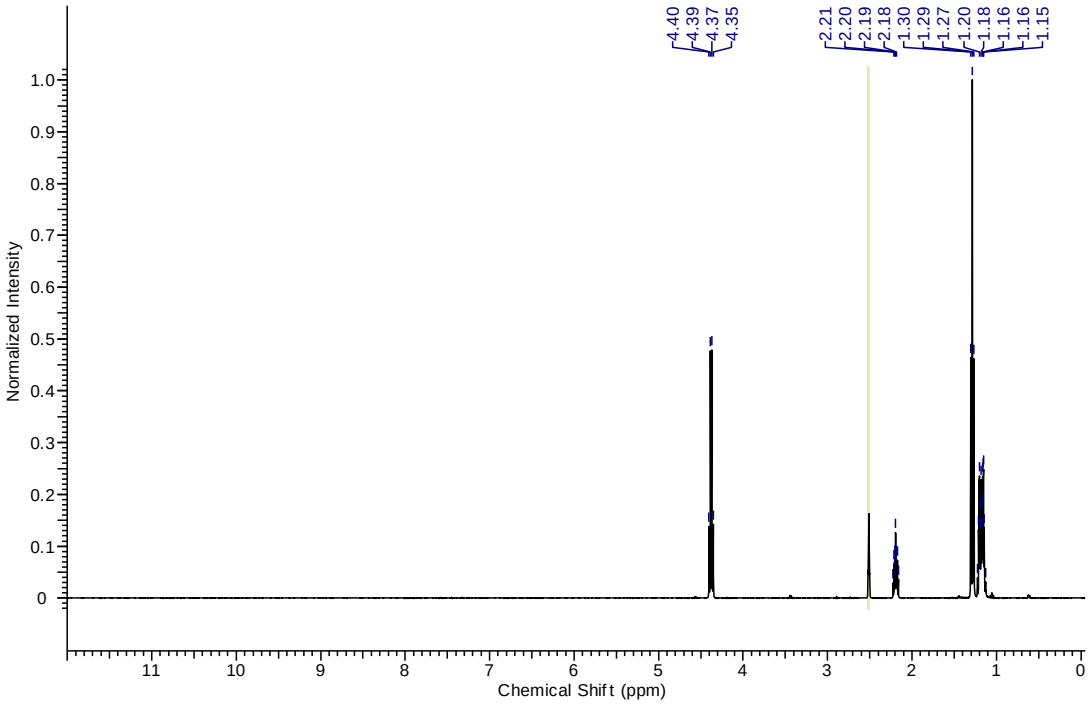


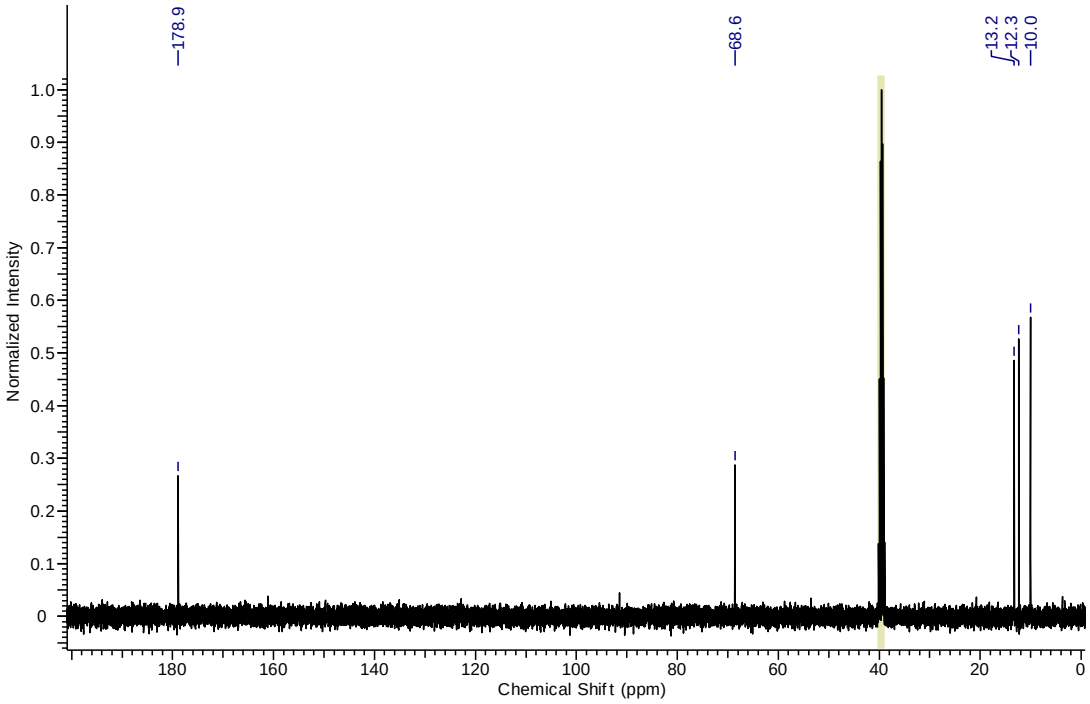




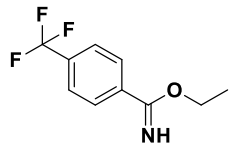
Cyclopropane carbimidate (78)

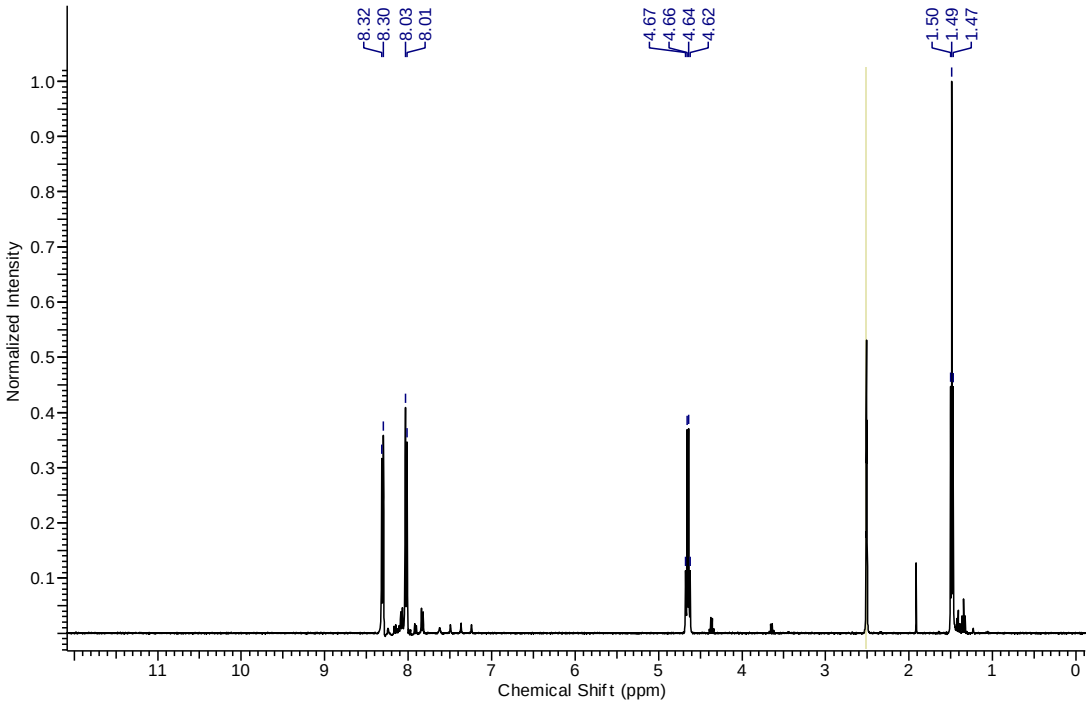


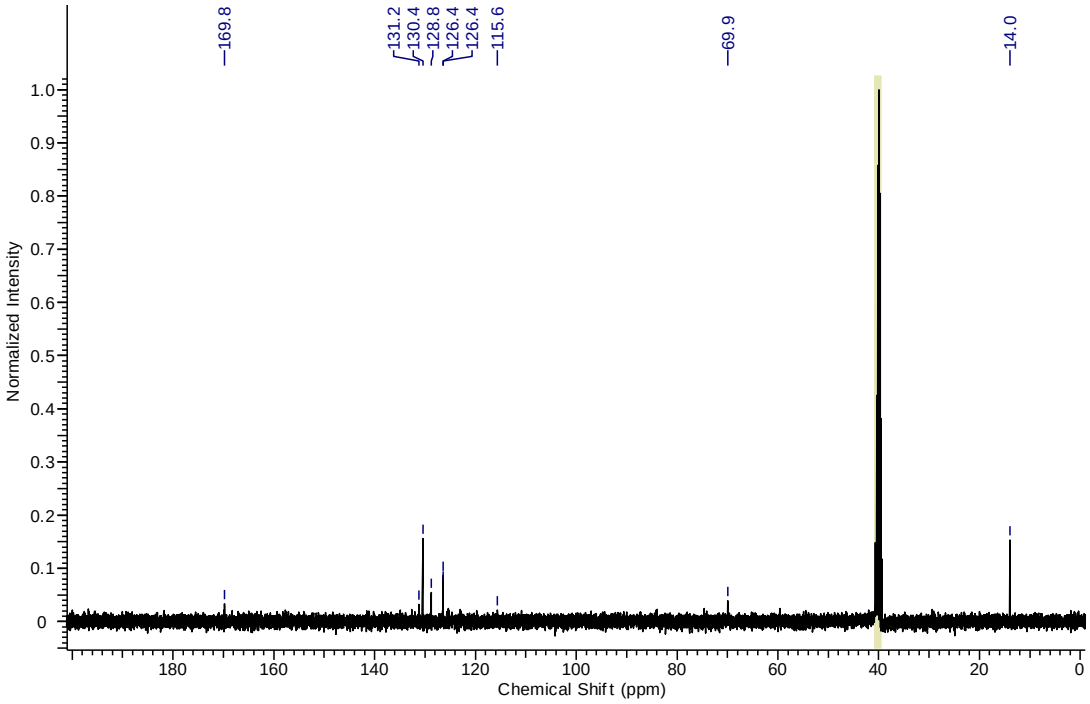




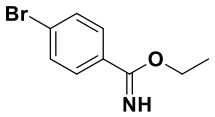
Ethyl 4-(trifluoromethyl)benzimidate (79)

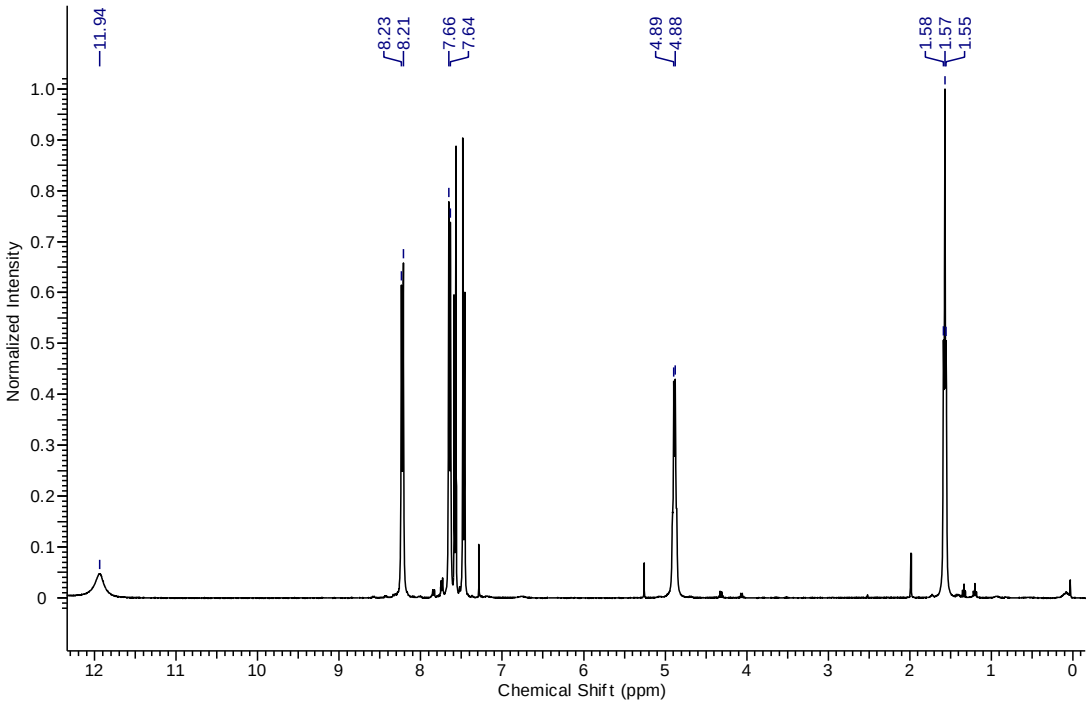


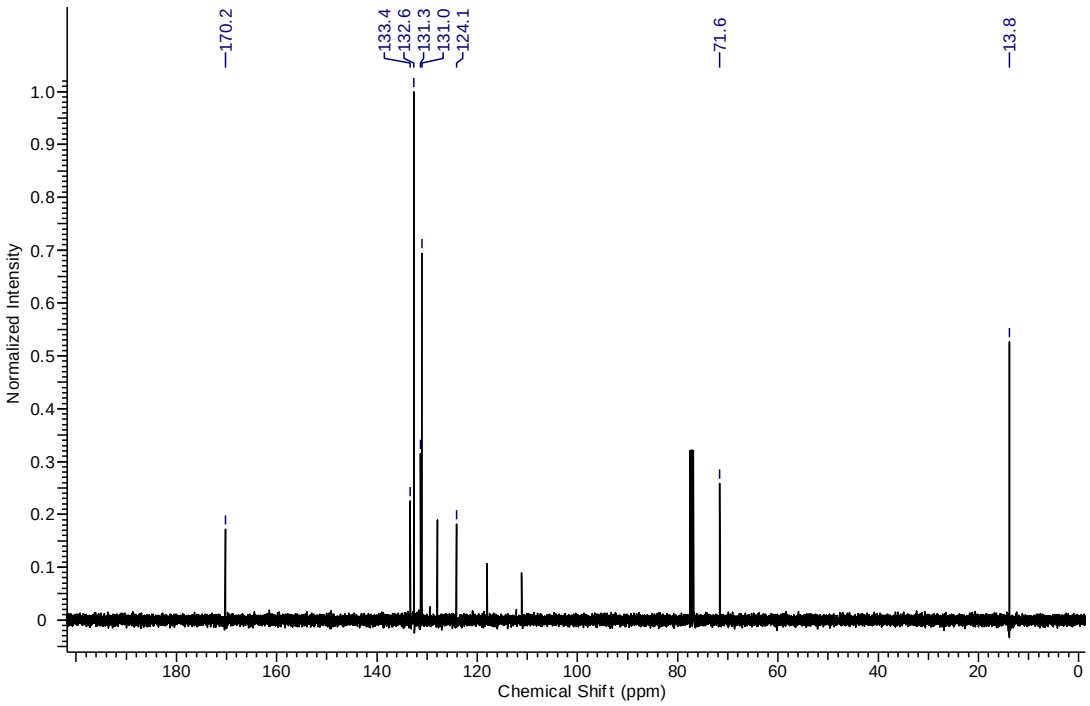




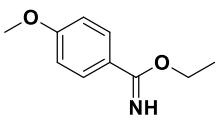
Ethyl 4-bromobenzimidate (80)

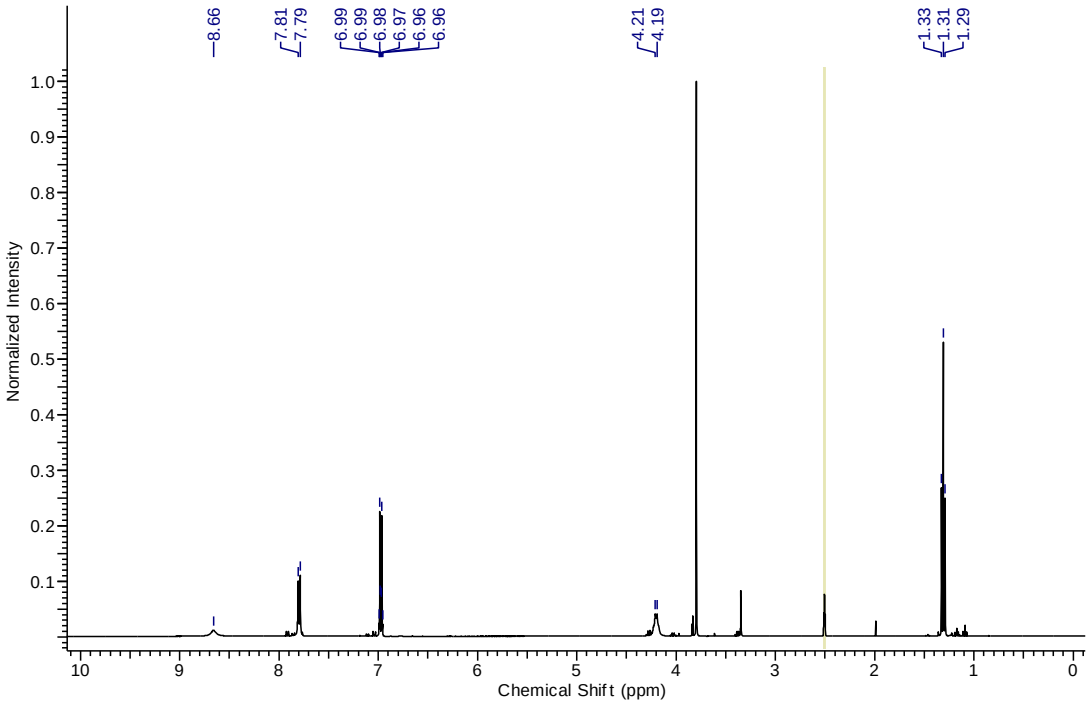


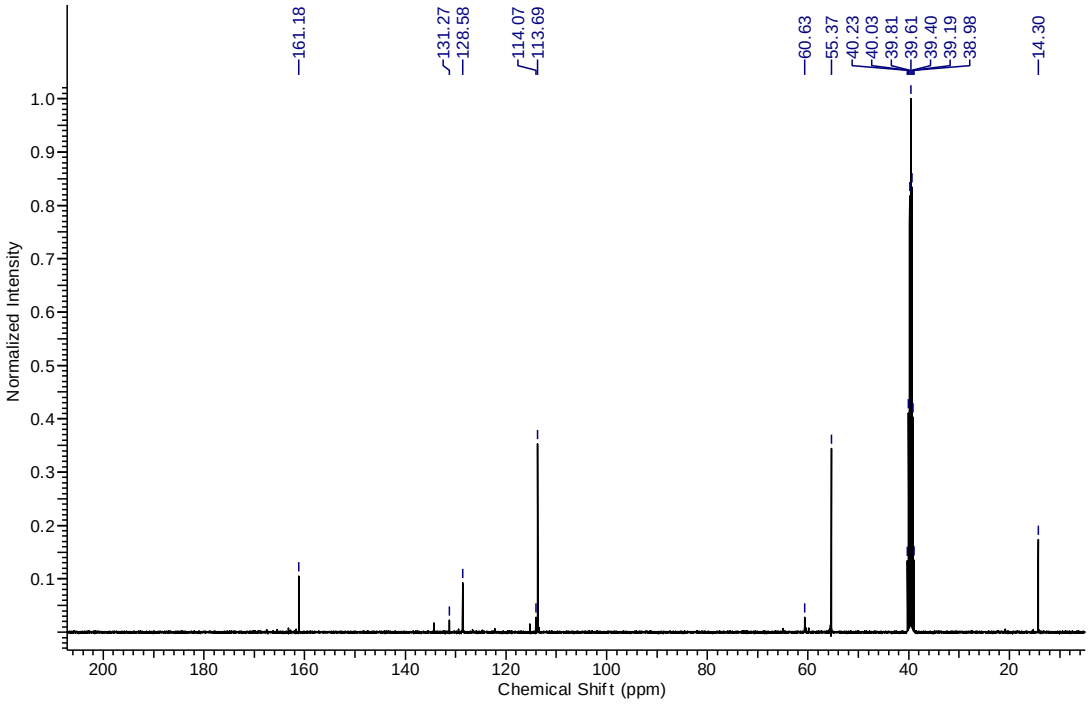




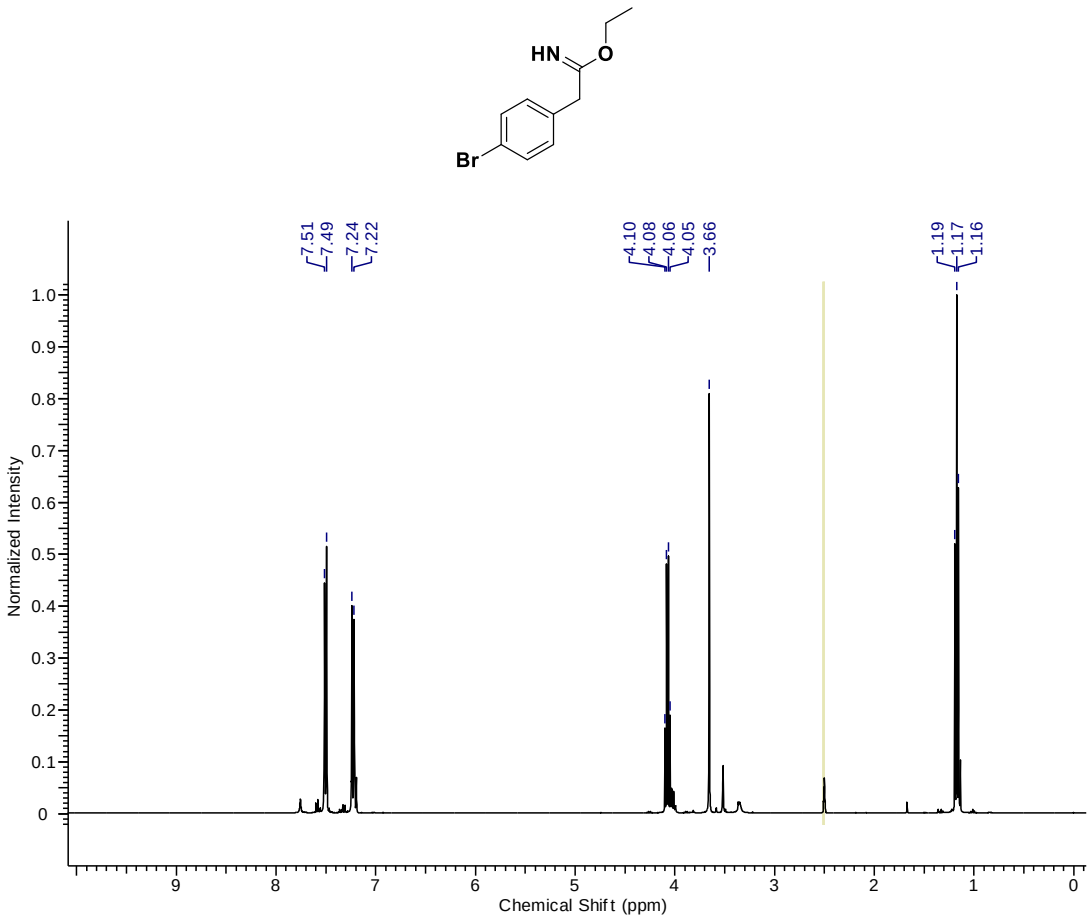
Ethyl 4-methoxybenzimidate (81)

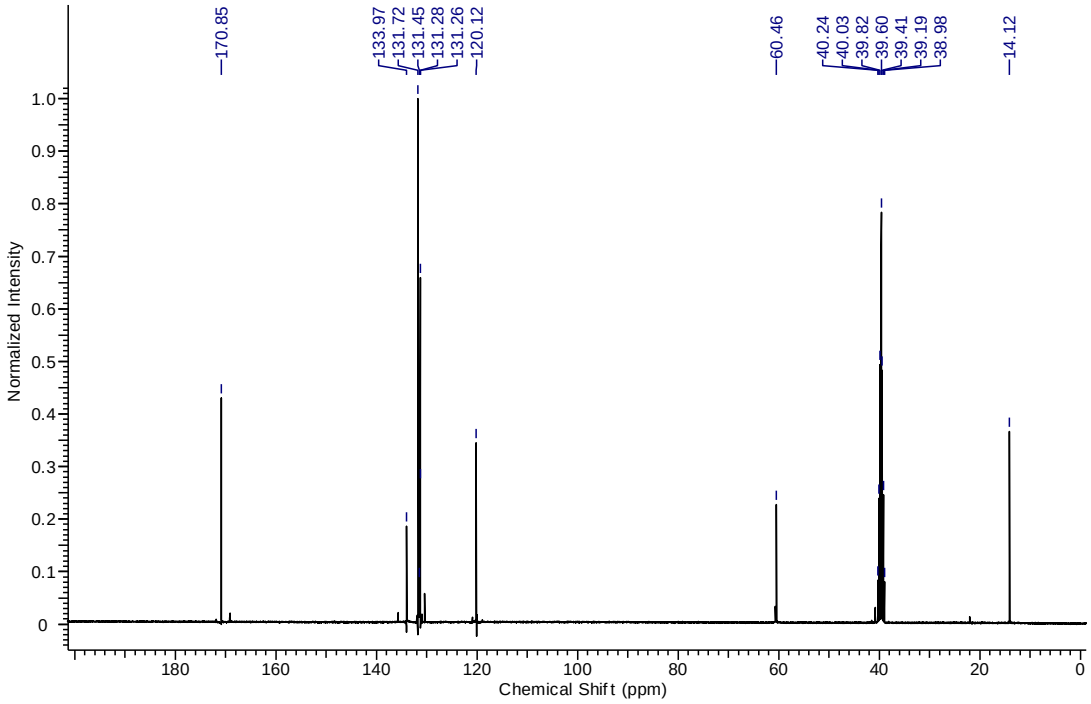




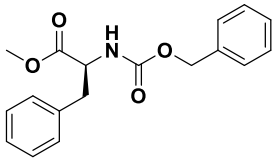


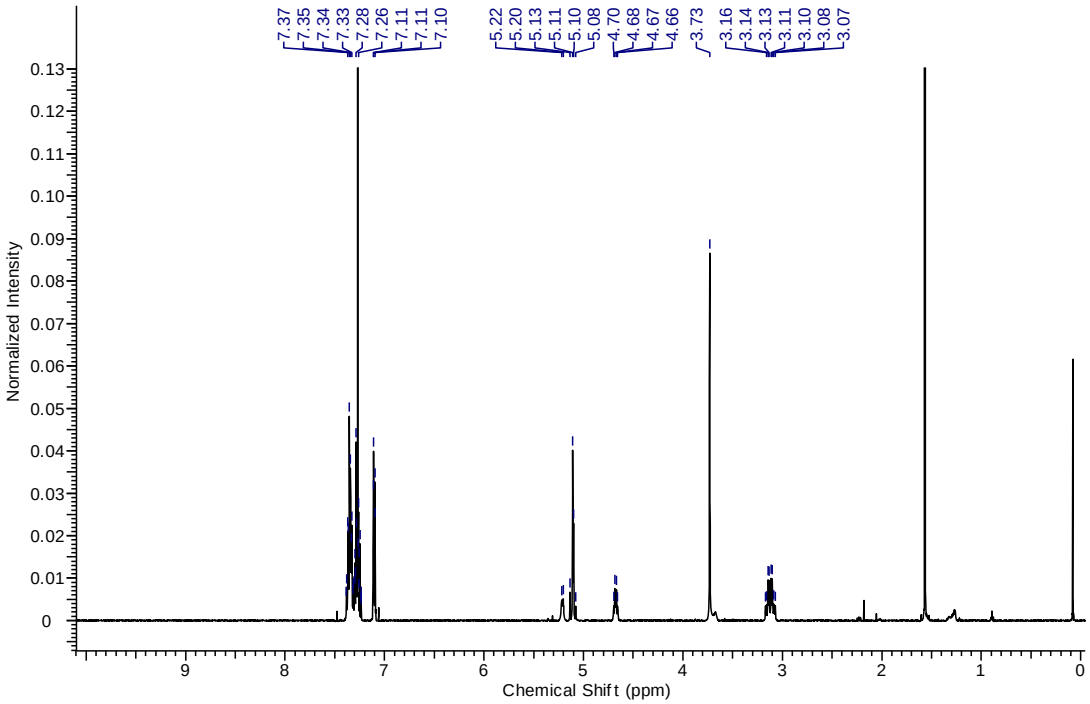
Ethyl 2-(4-bromophenyl)acetimidate (82)

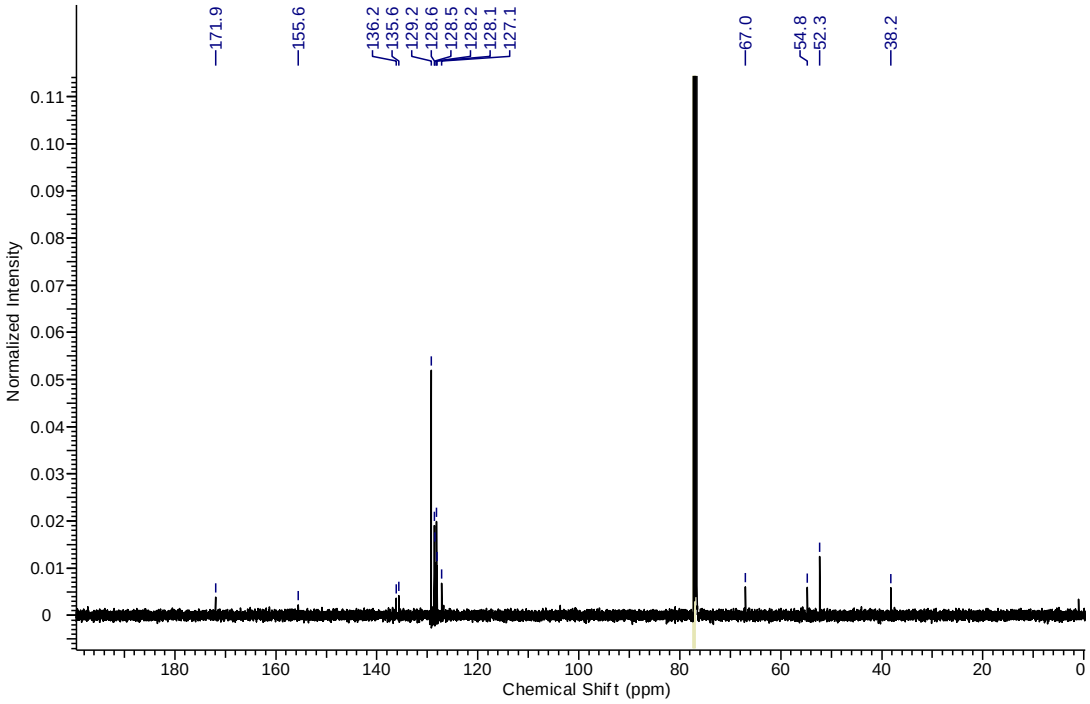




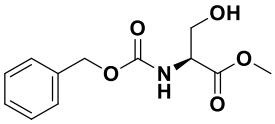
Methyl((benzyloxy)carbonyl)-L- phenylalaninate (51)

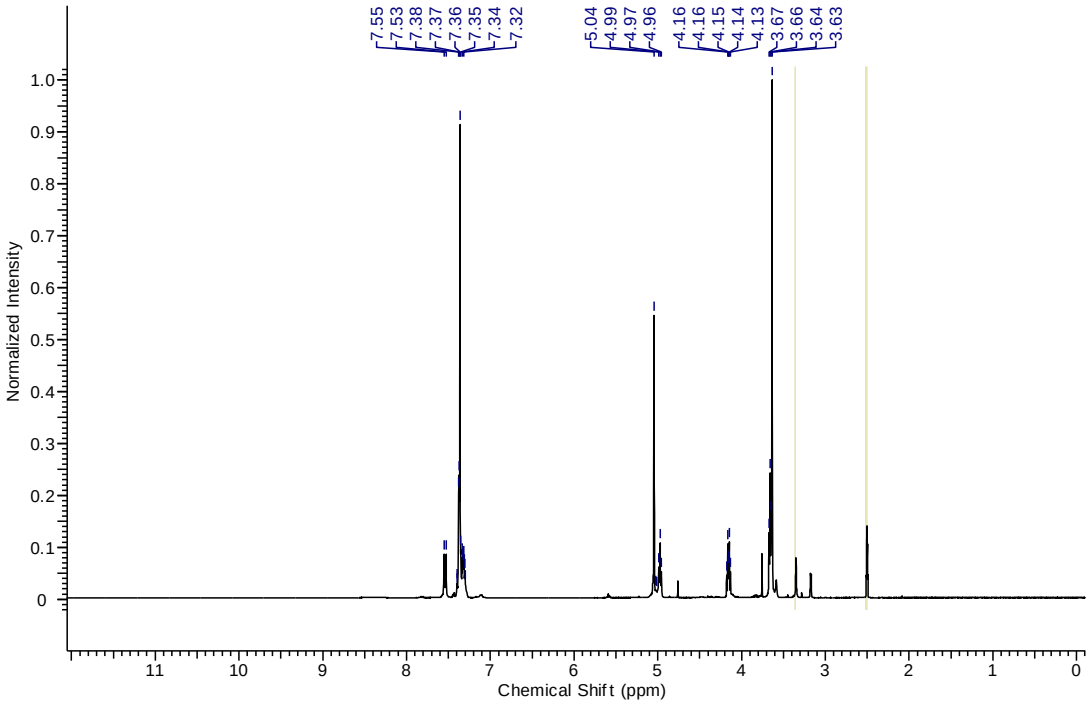


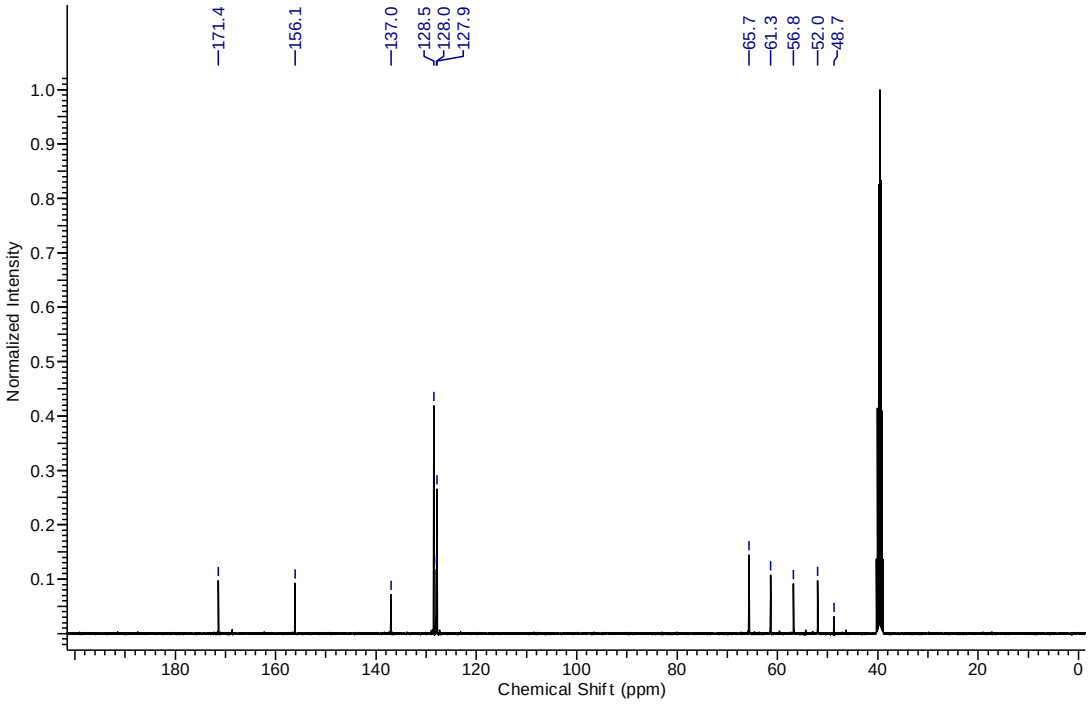




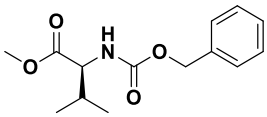
Methyl ((benzyloxy)carbonyl)-L-serinate (89)

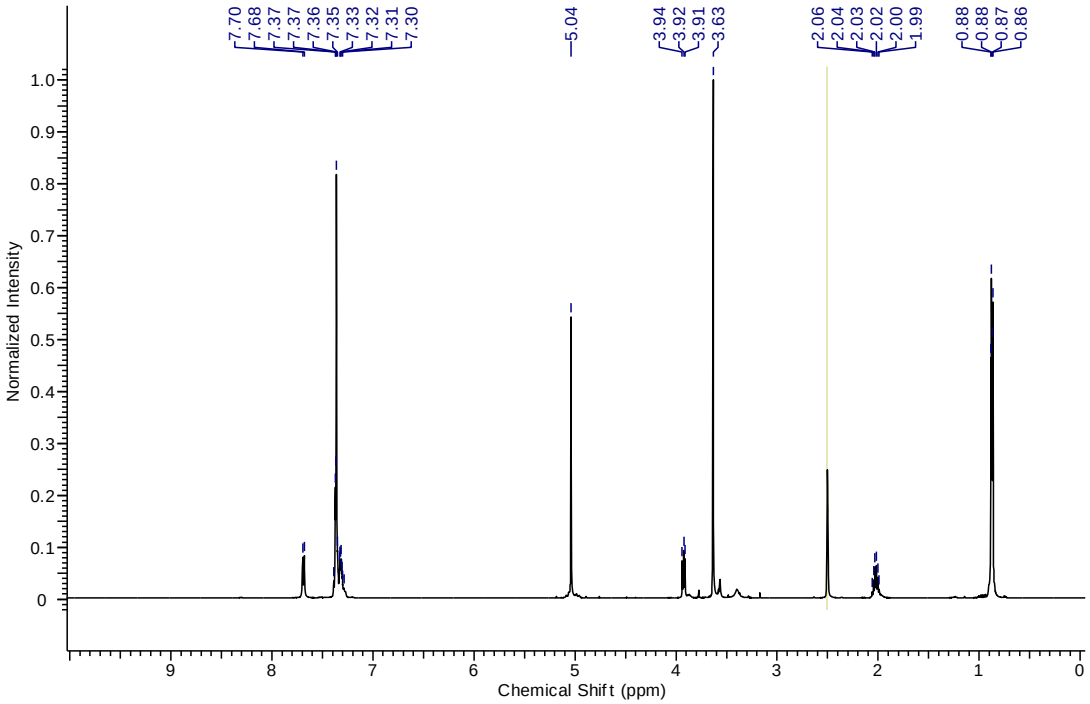


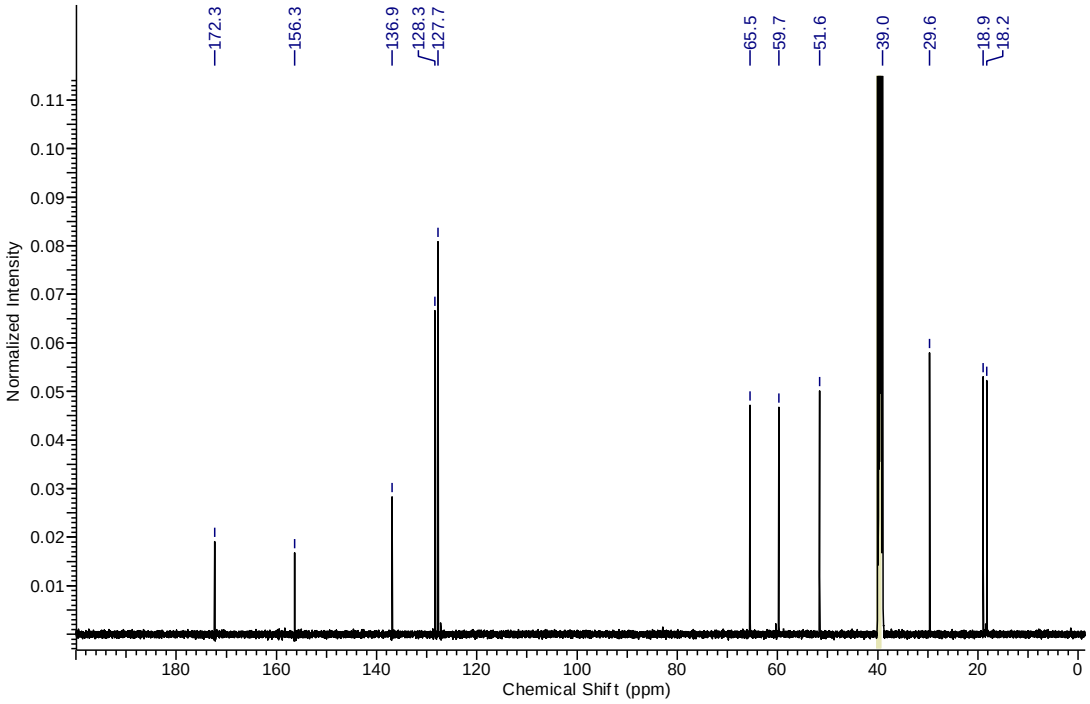




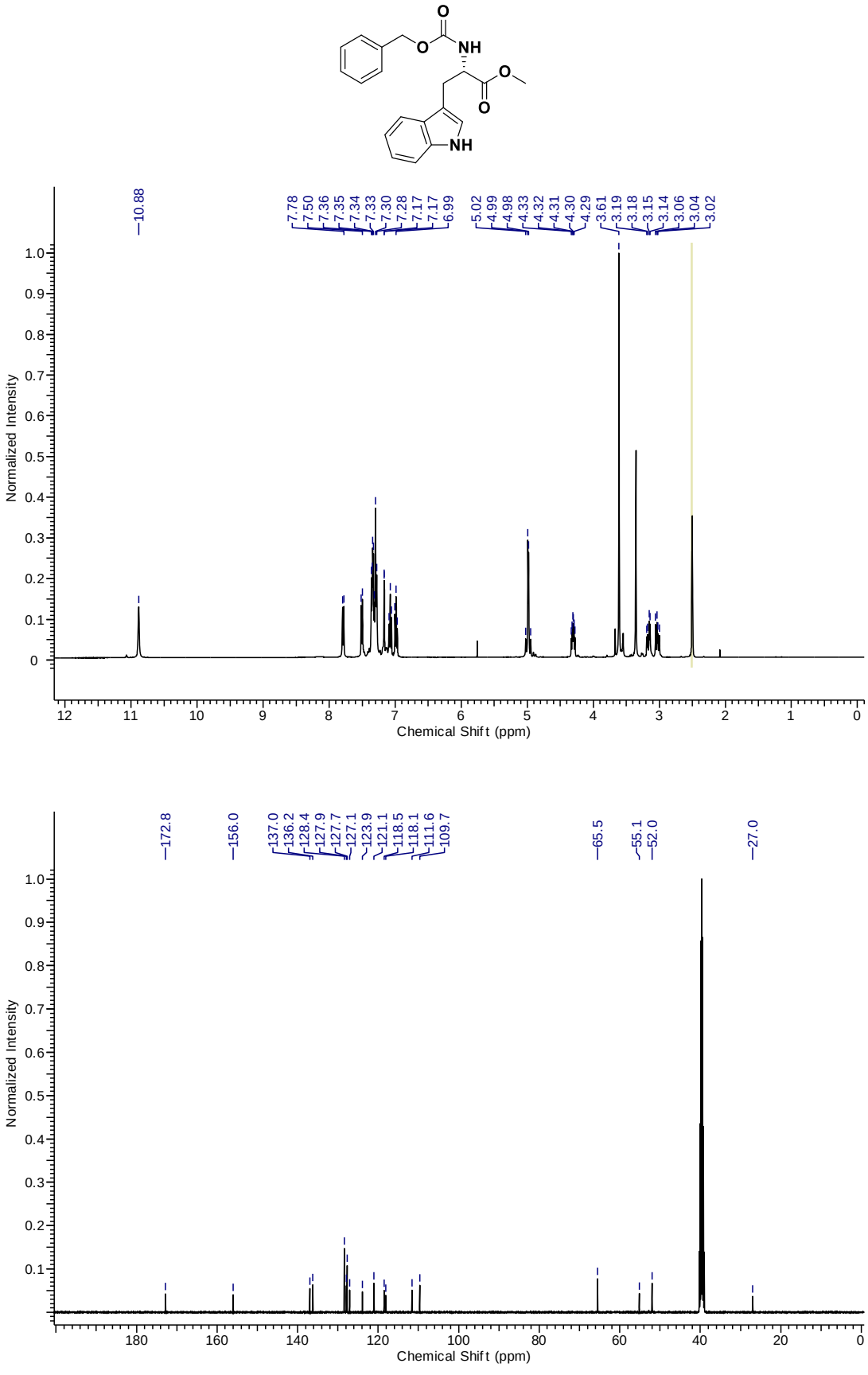
Methyl ((benzyloxy)carbonyl)-L-valinate (90)



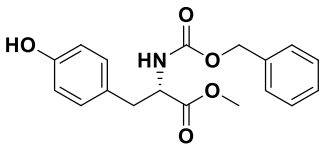


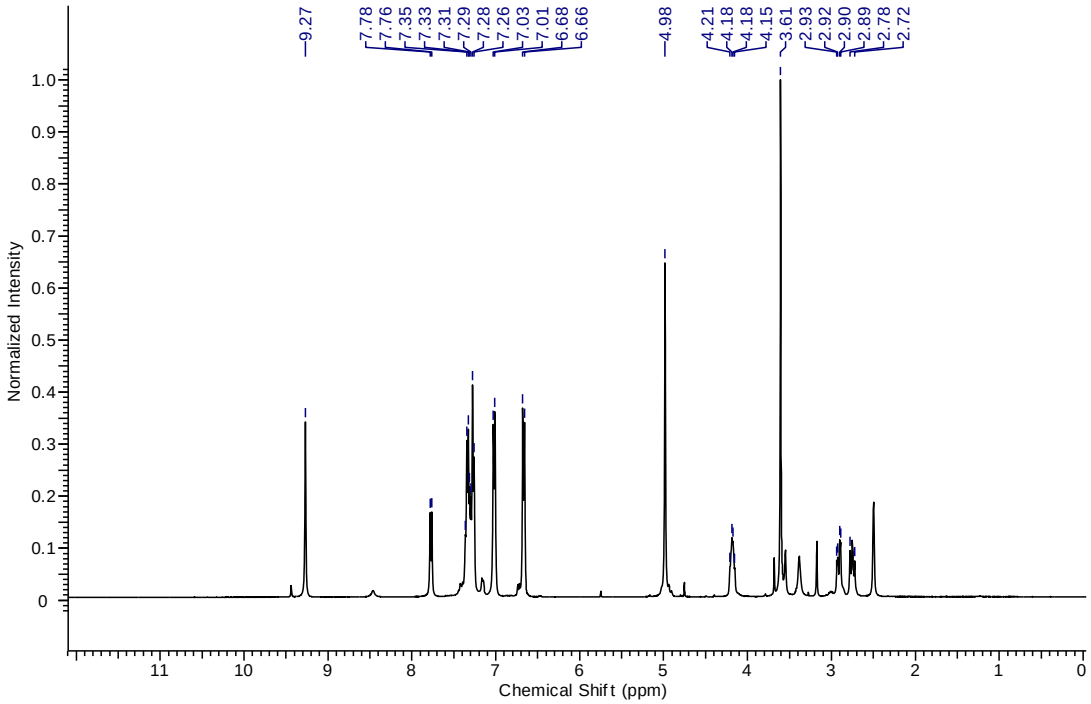


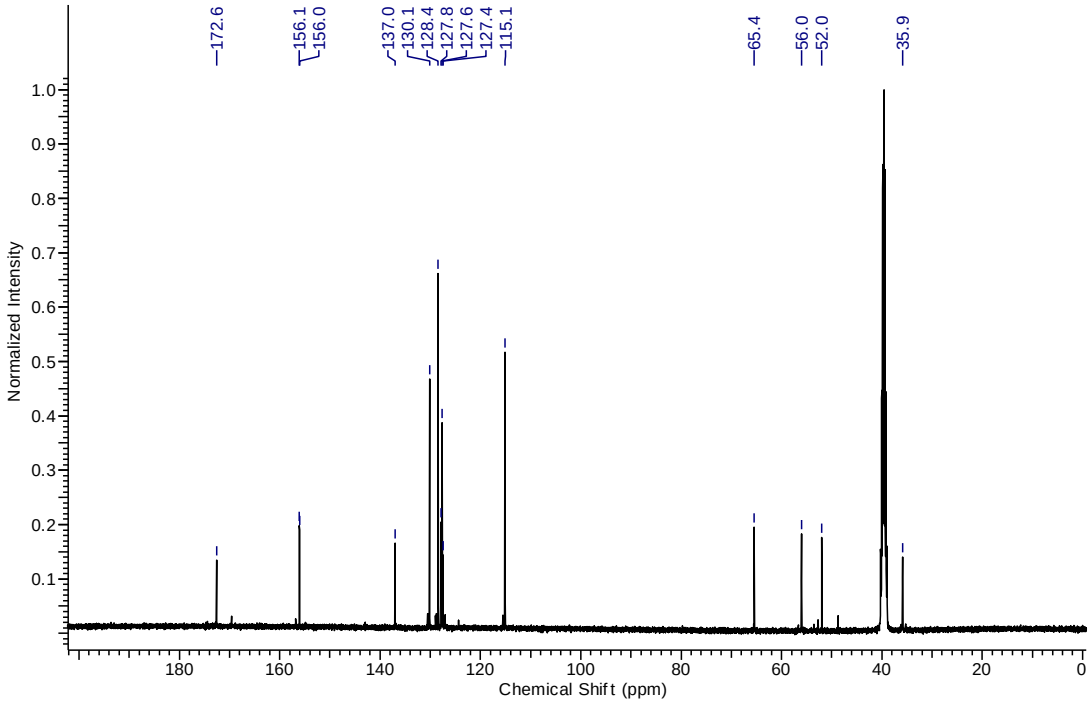
Methyl ((benzyloxy)carbonyl)-L-tryptophanate (91)



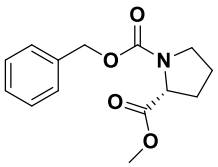
Methyl ((benzyloxy)carbonyl)-L-tyrosinate (92)

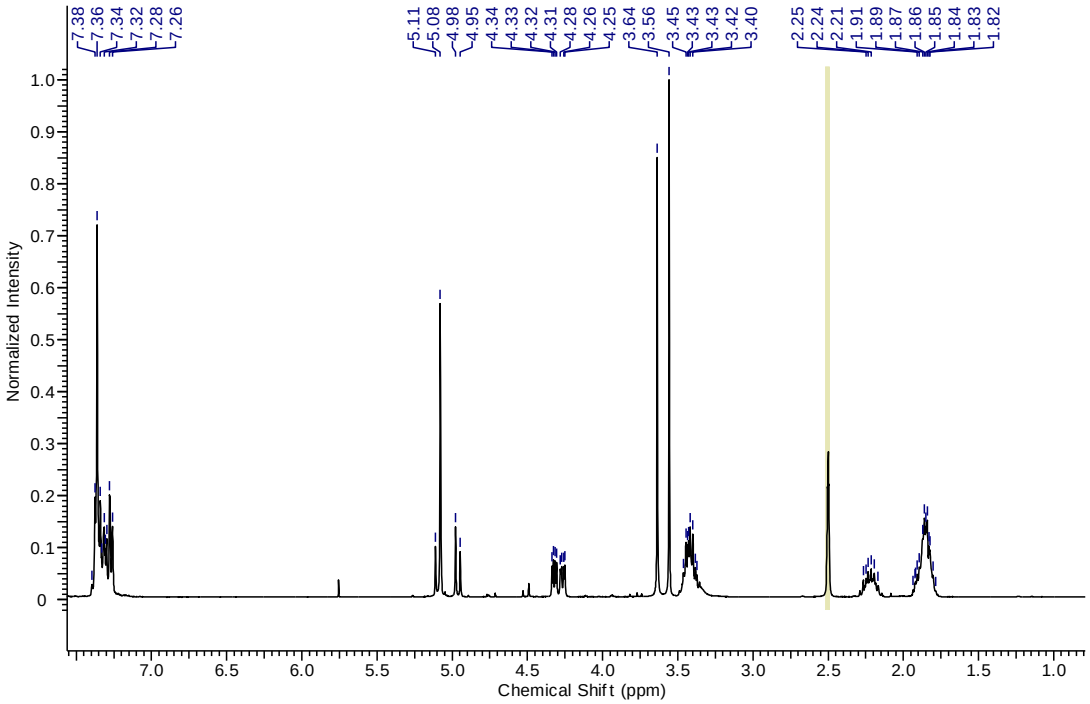


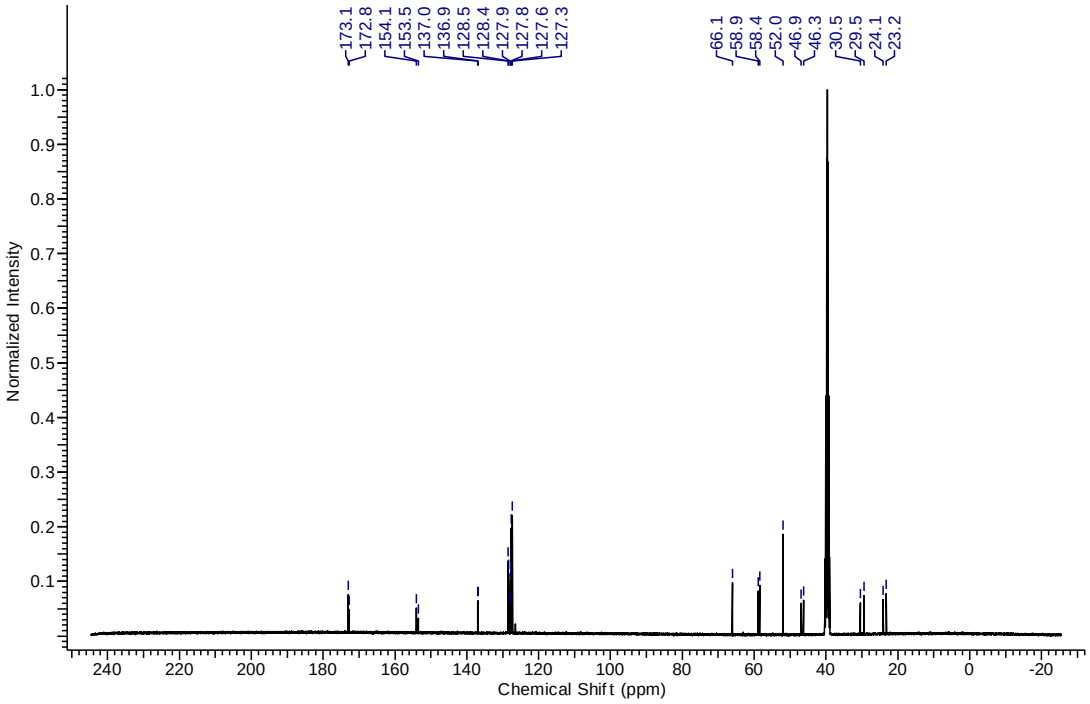




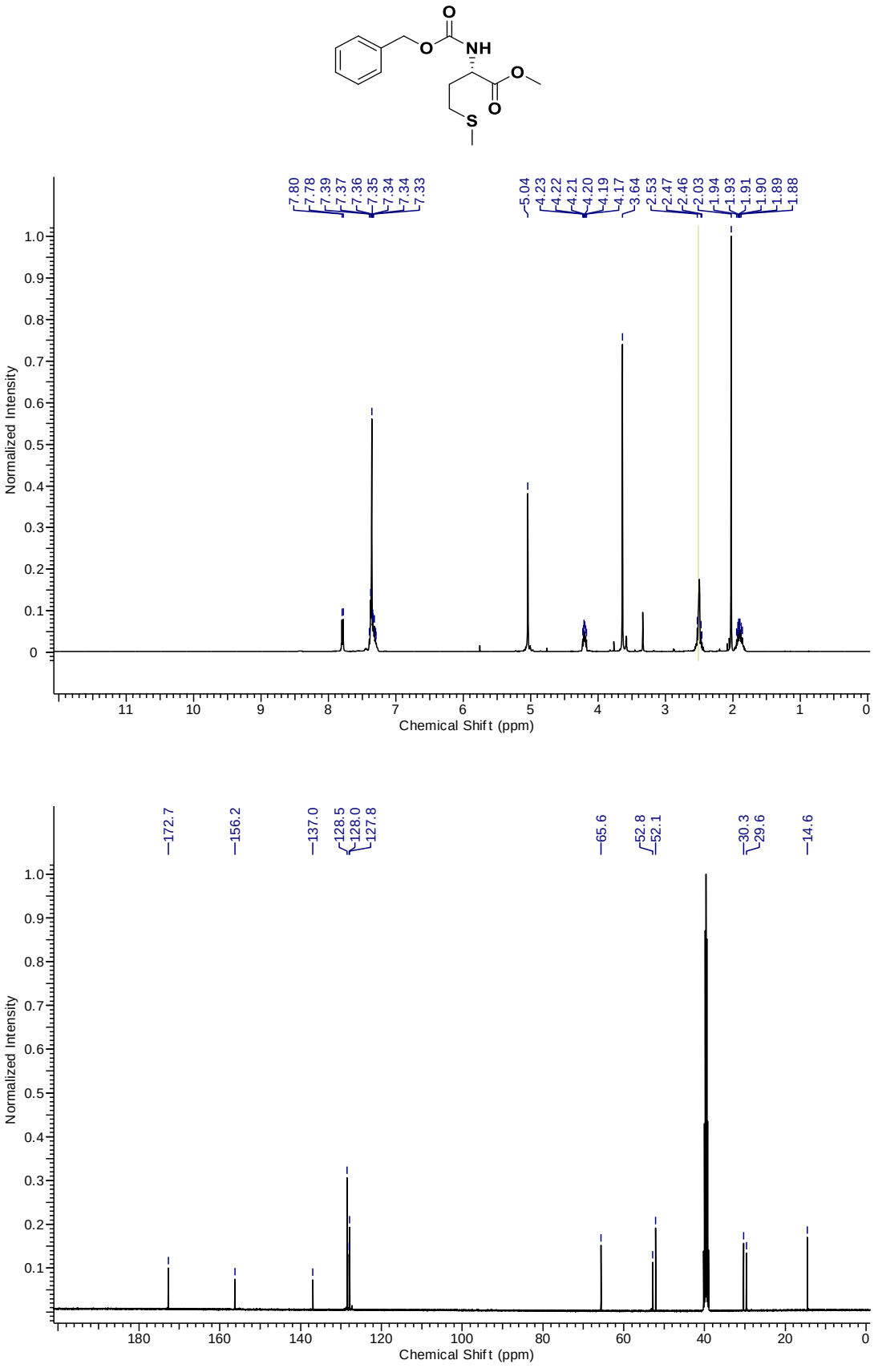
Methyl ((benzyloxy)carbonyl)-L-prolinate (93)



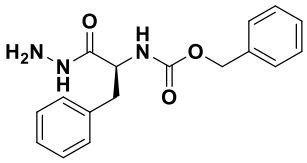


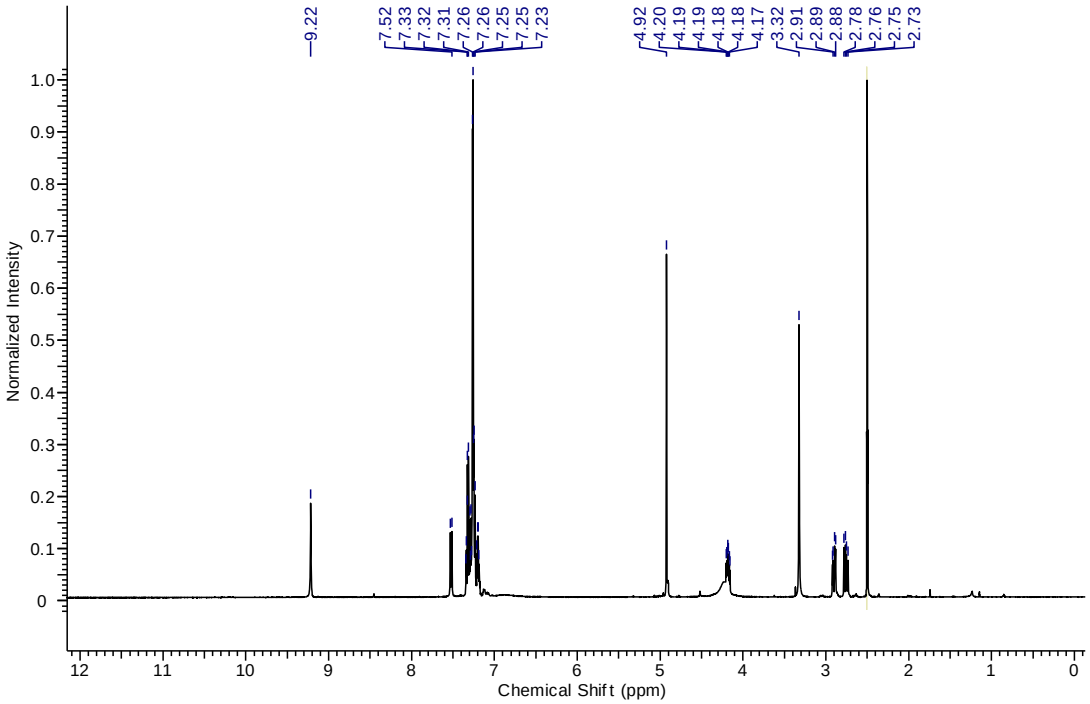


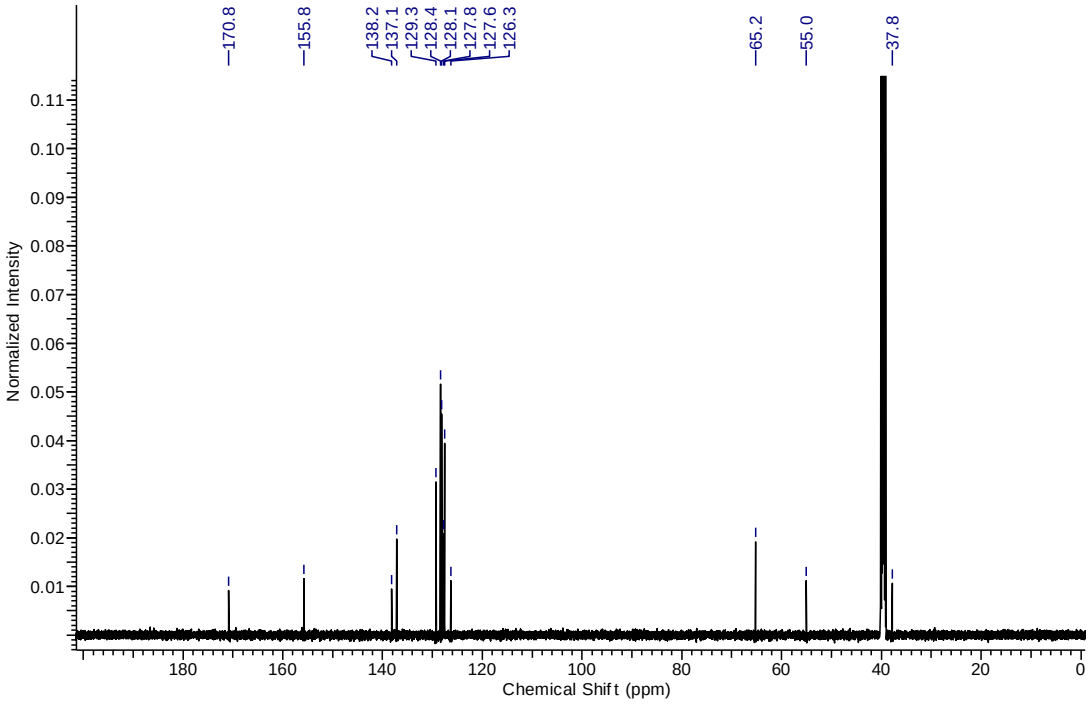
Methyl ((benzyloxy)carbonyl)-L-methioninate (94)



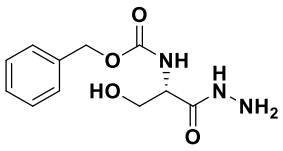
Benzyl (S)-(1-hydrazinyl-1-oxo-3-phenylpropan-2-yl)carbamate (52)

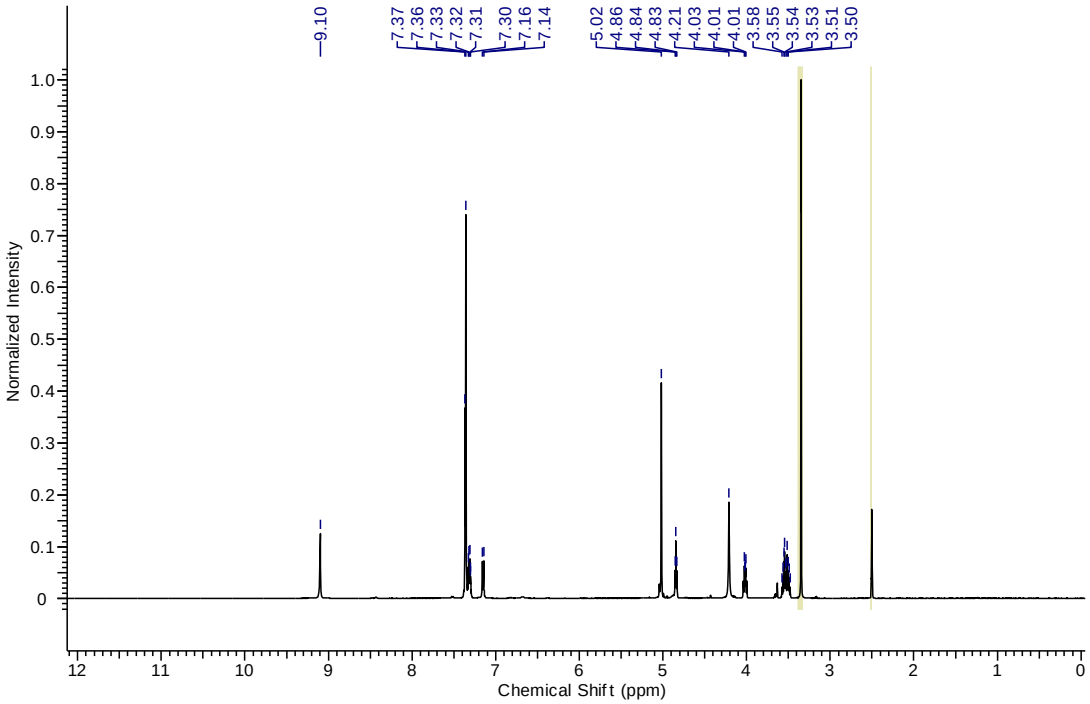


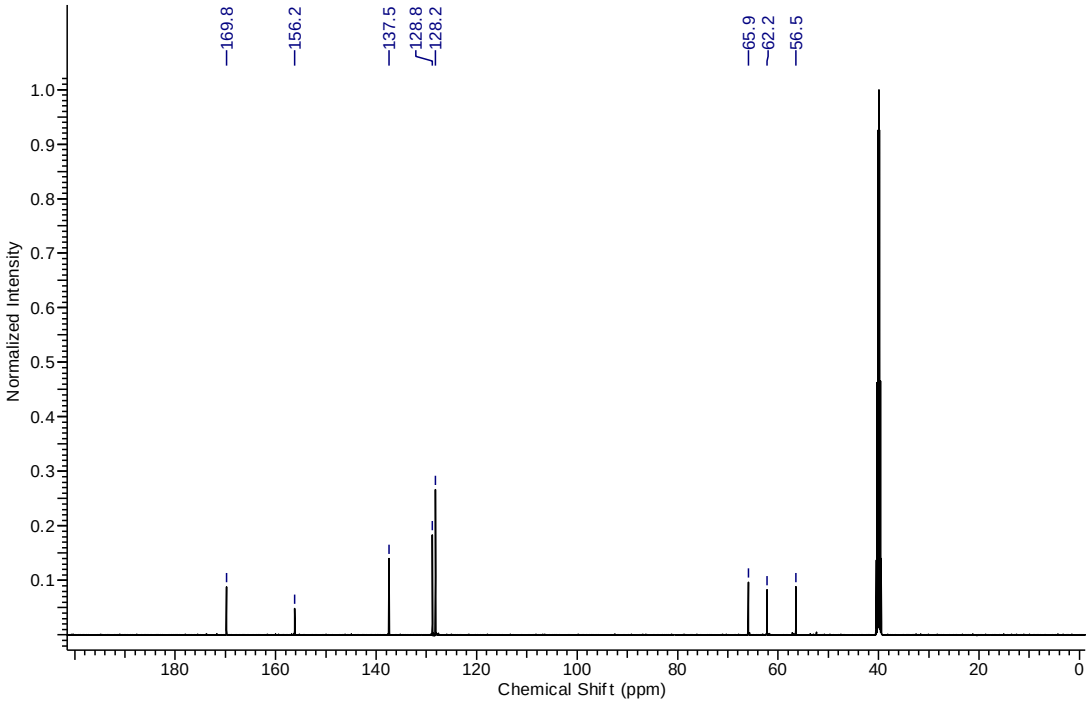




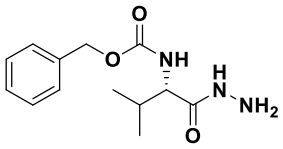
Benzyl (S)-(1-hydrazinyl-3-hydroxy-1-oxopropan-2-yl)carbamate (95)

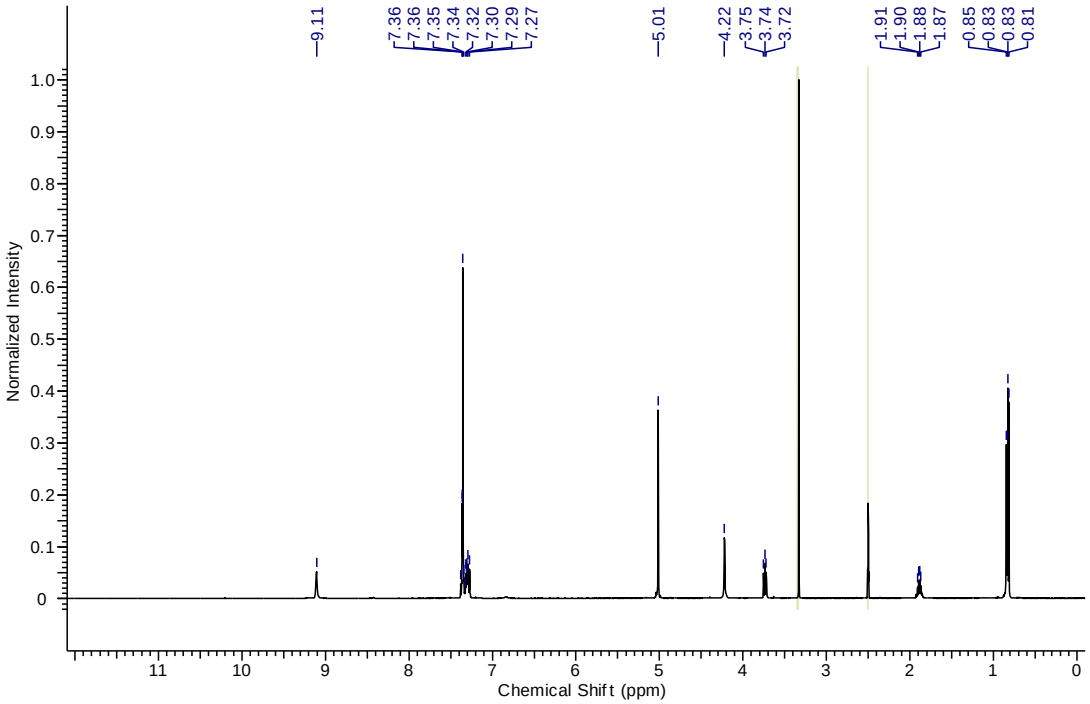


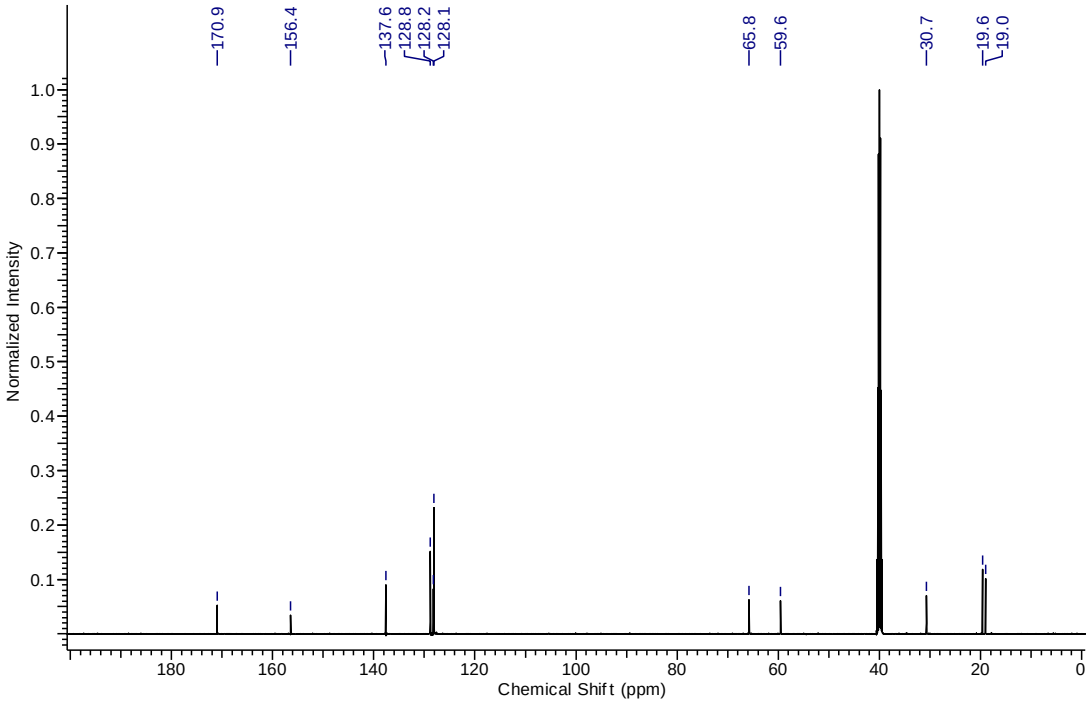




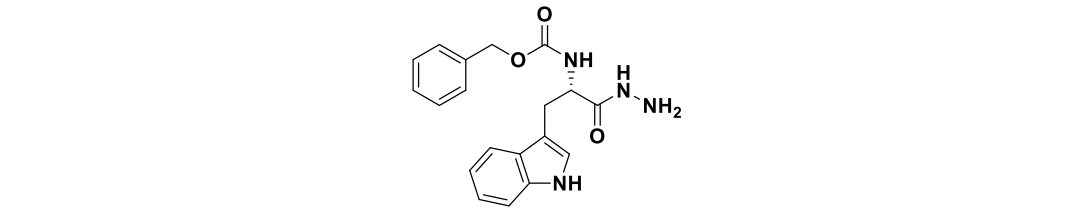
Benzyl (S)-(1-hydrazinyl-3-methyl-1-oxobutan-2-yl)carbamate (96)

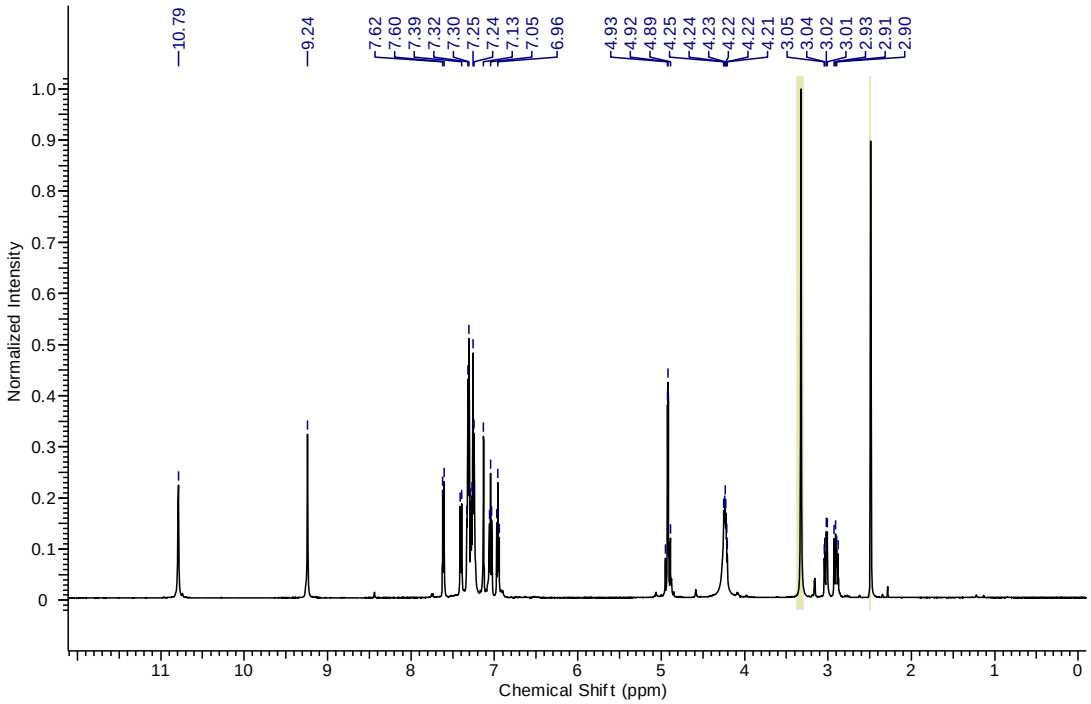


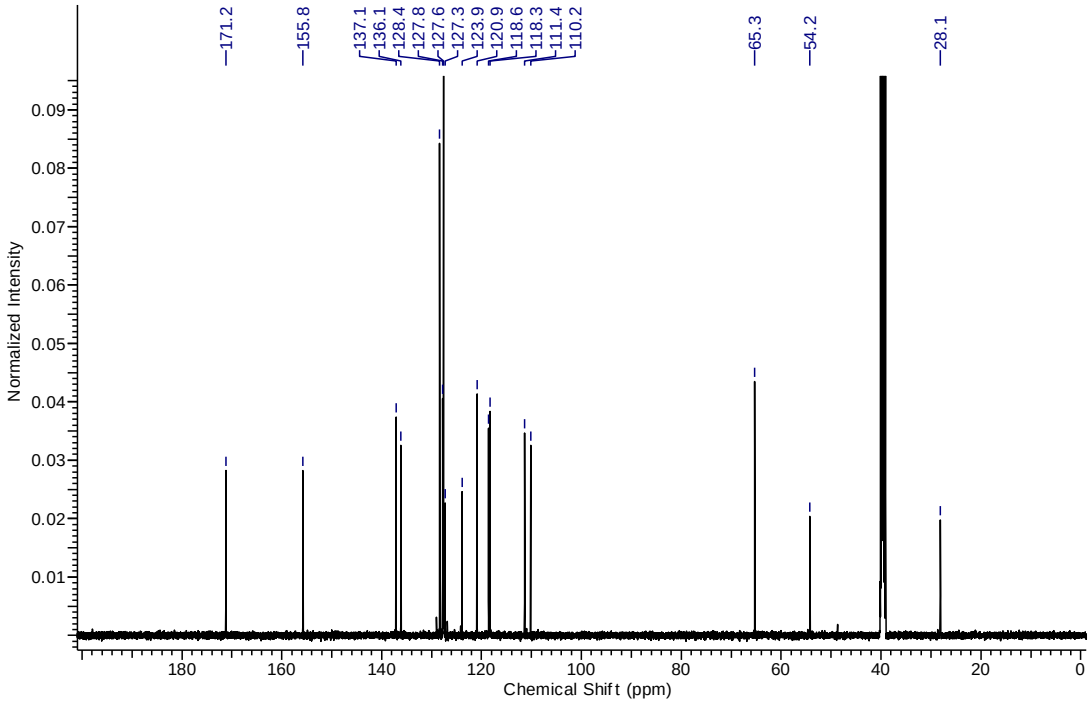




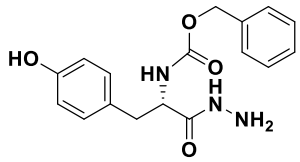
Benzyl (S)-(1-hydrazinyl-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate (97)

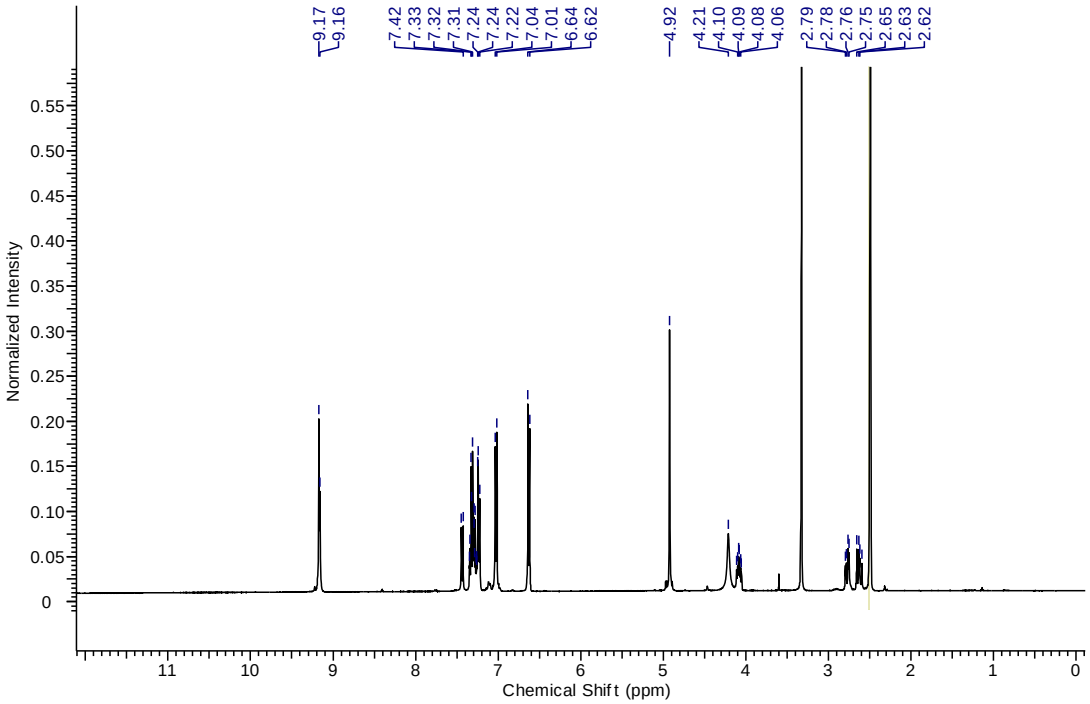


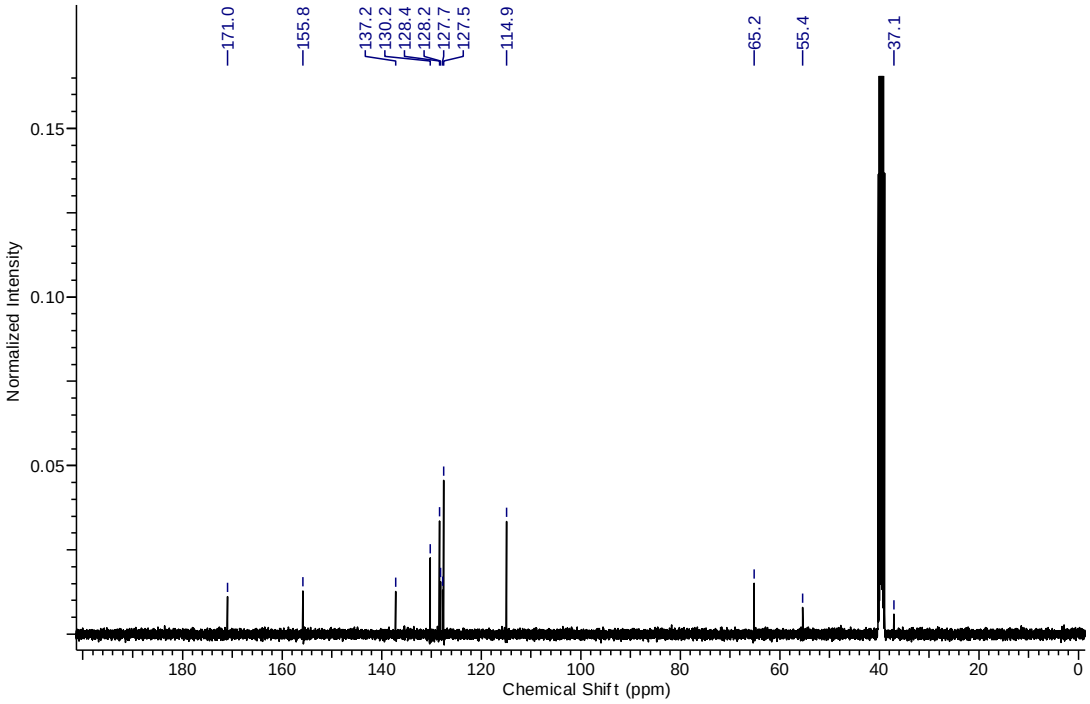




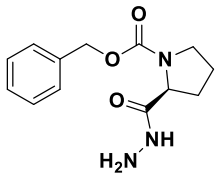
Benzyl (S)-(1-hydrazinyl-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamate

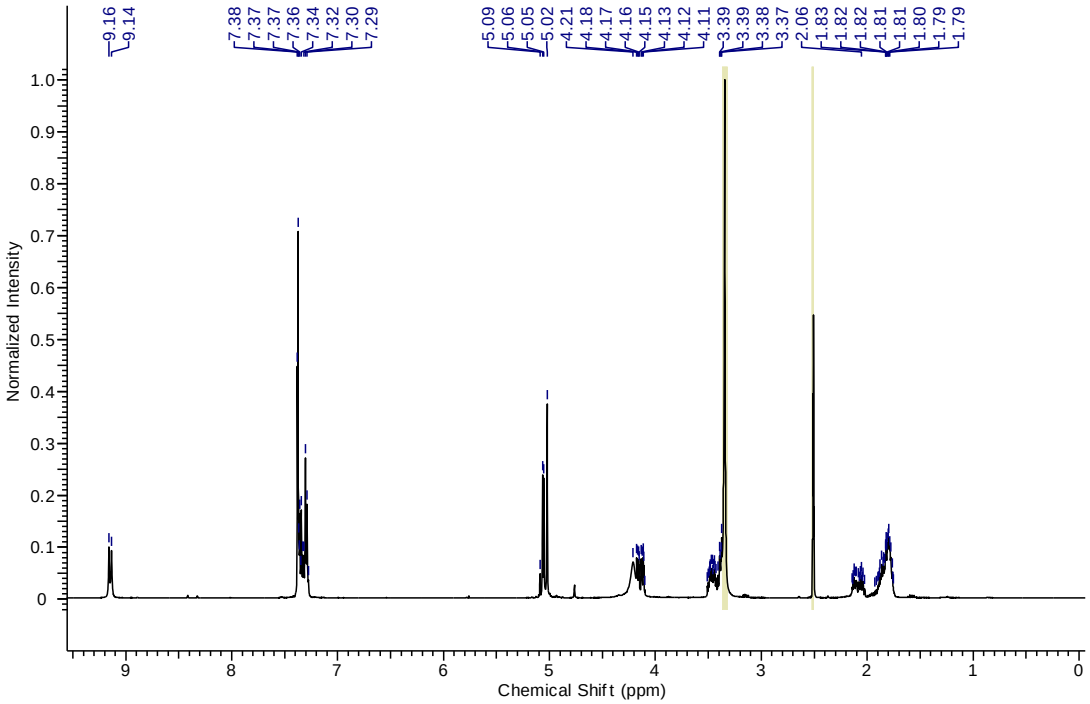


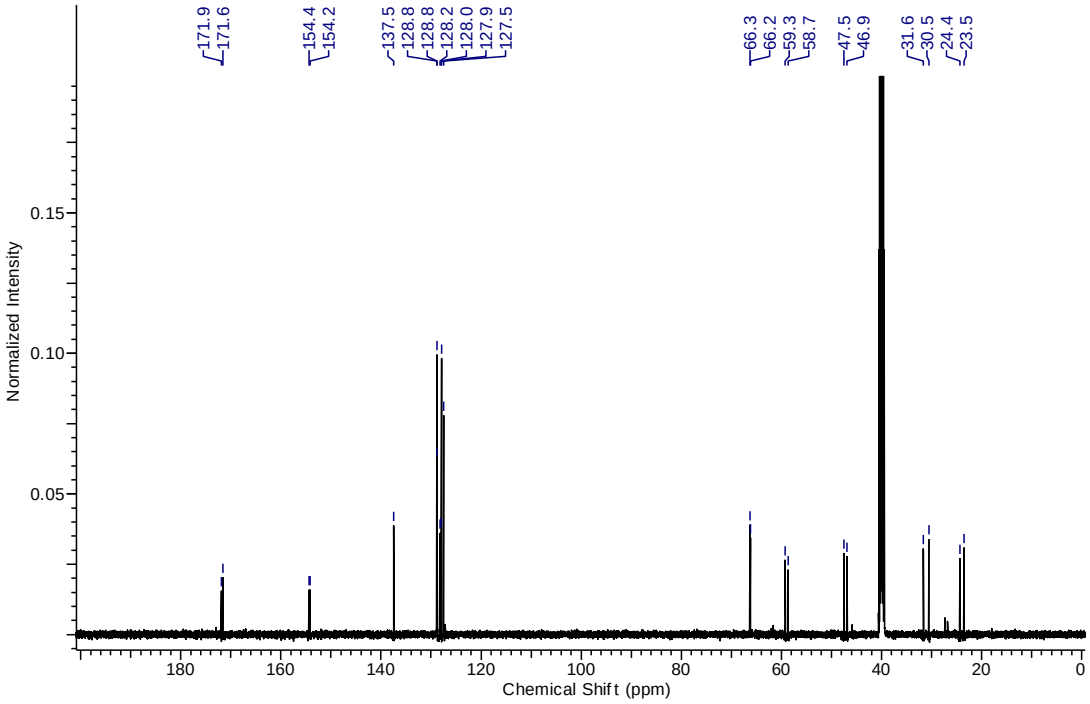




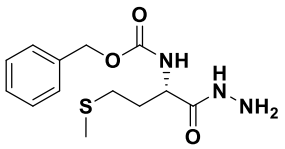
Benzyl (S)-2-(hydrazinecarbonyl)pyrrolidine-1-carboxylate (99)

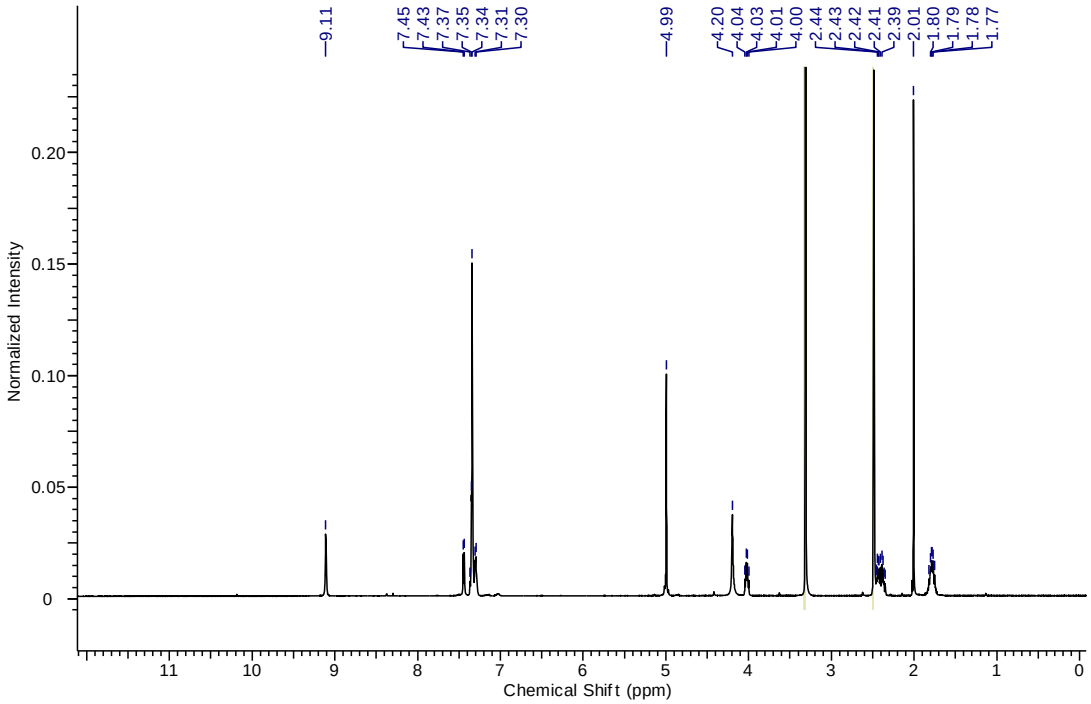


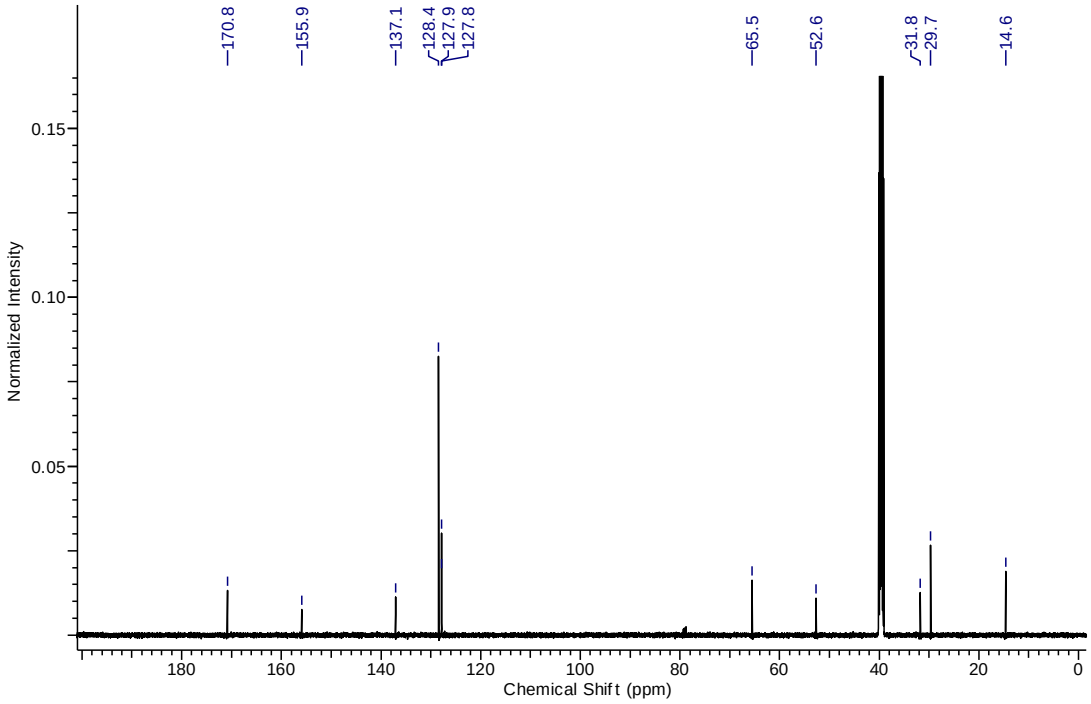




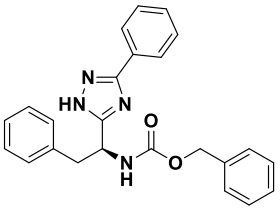
Benzyl (S)-(1-hydrazinyl-4-(methylthio)-1-oxobutan-2-yl)carbamate (100)

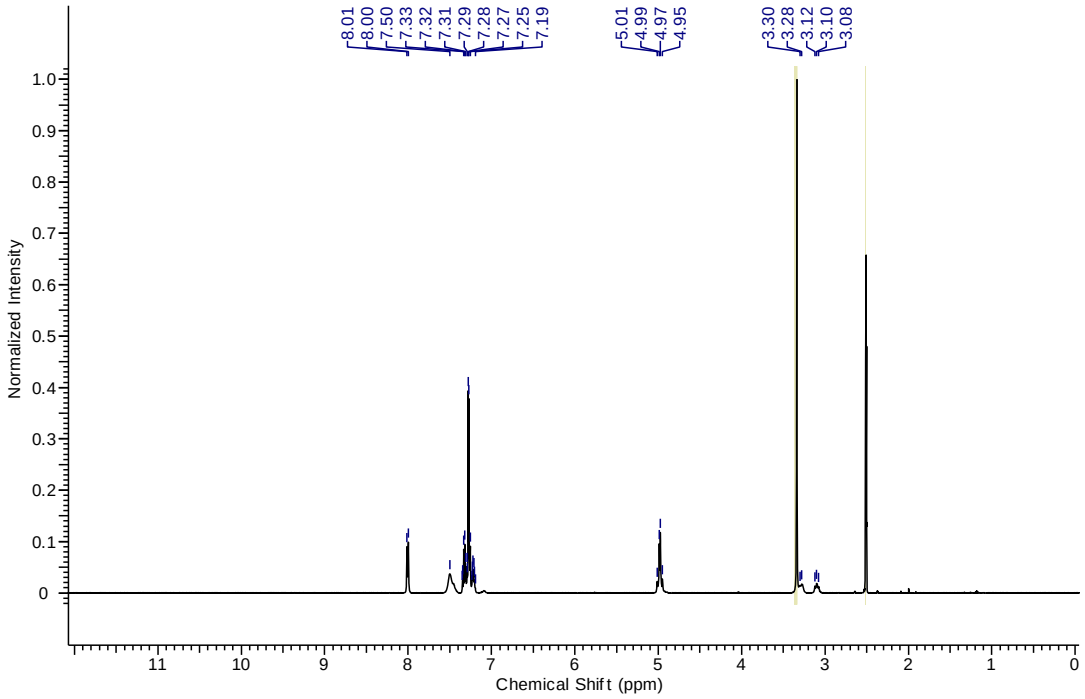


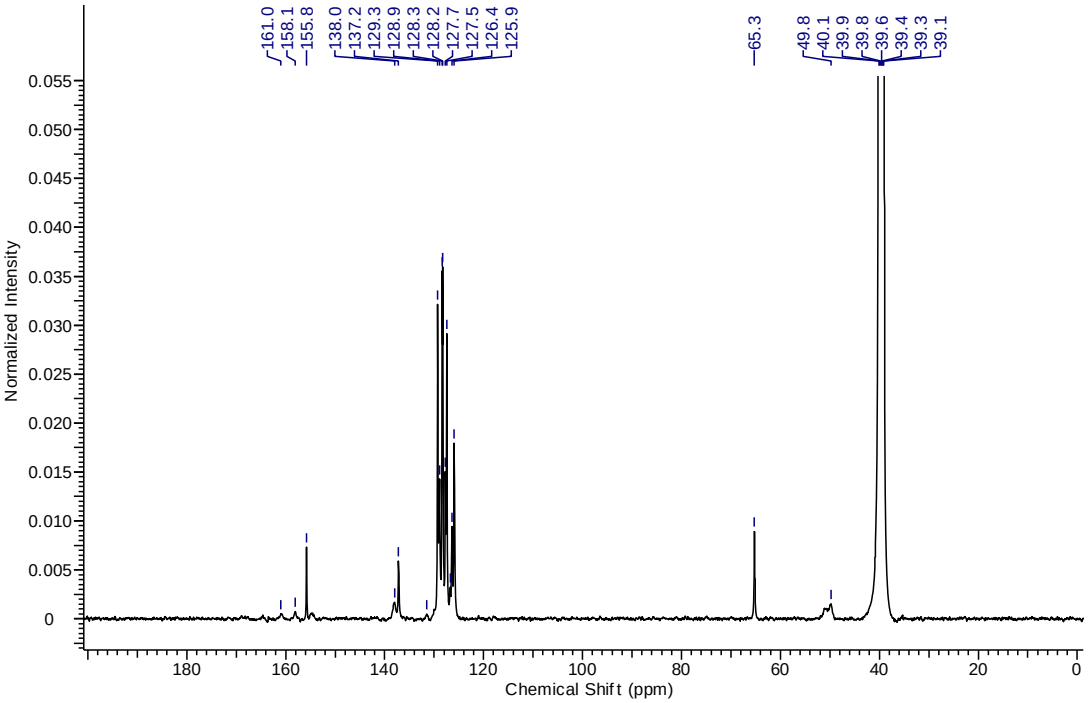




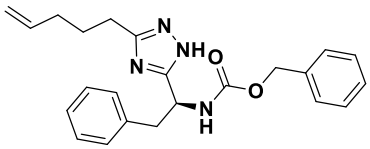
Benzyl (*S*)-(2-phenyl-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate (54)

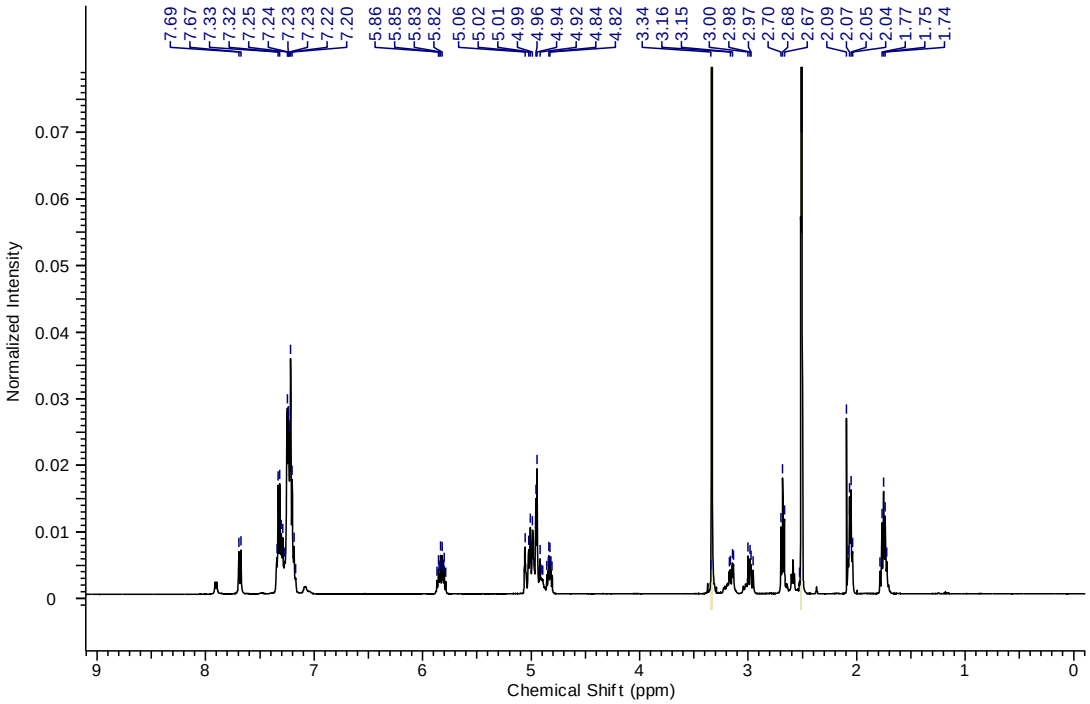


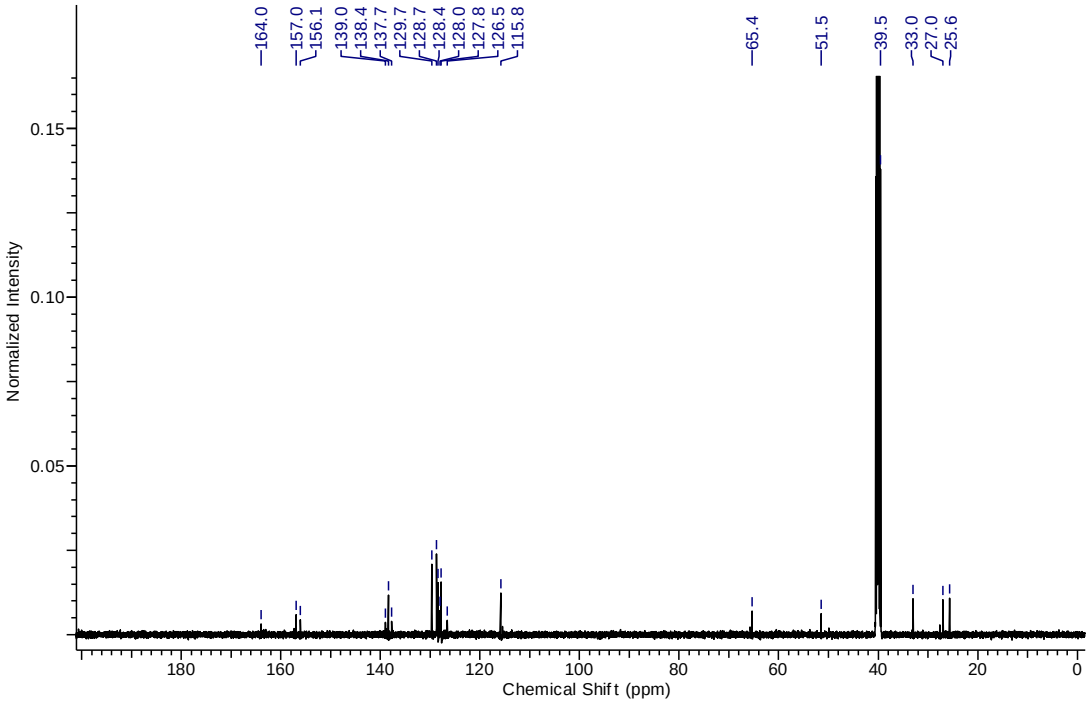




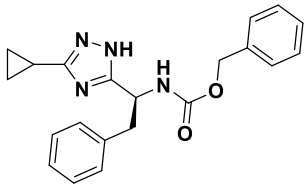
Benzyl (S)-(1-(3-(pent-4-en-1-yl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate

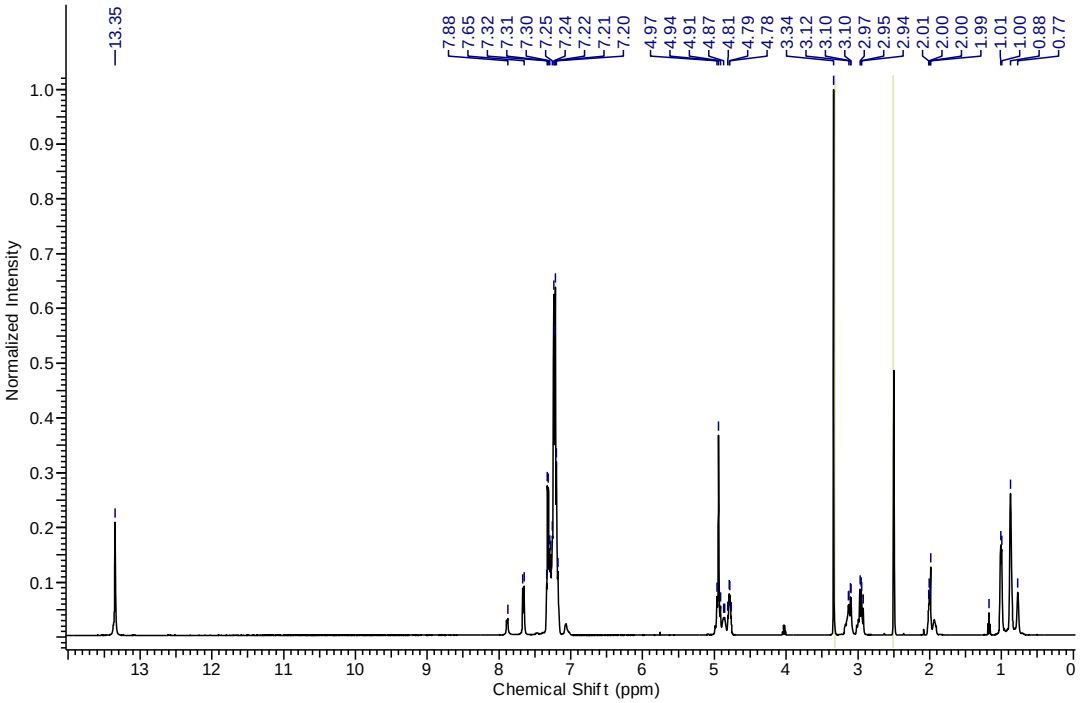


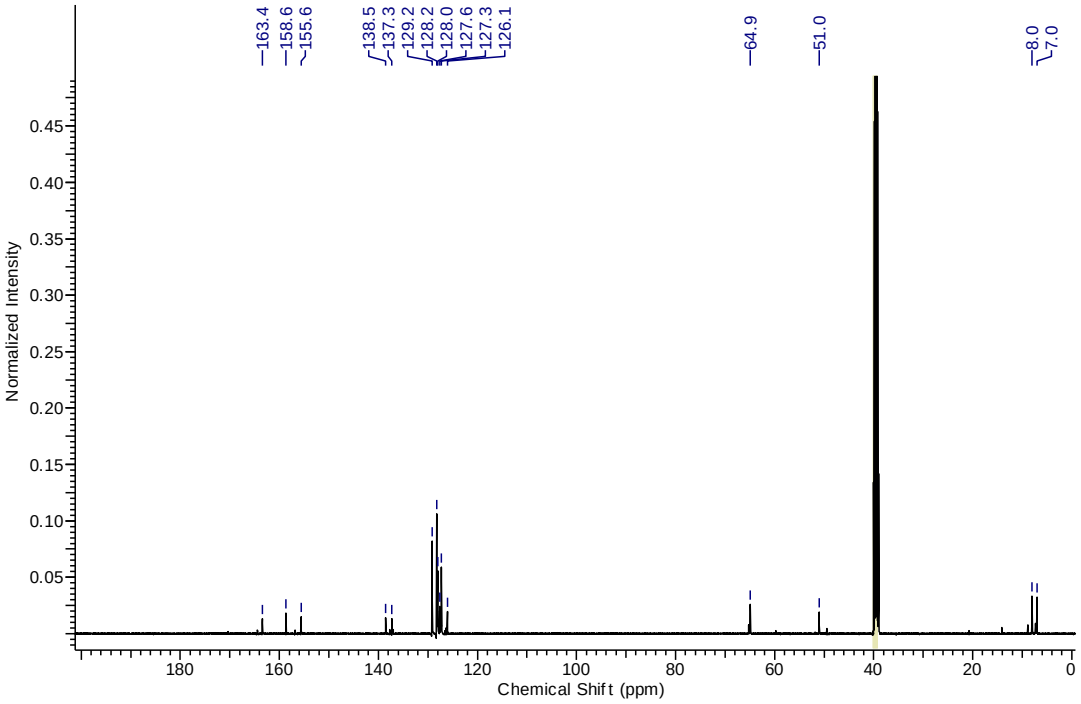




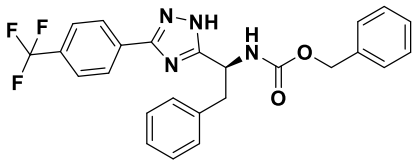
Benzyl (S)-(1-(3-cyclopropyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (102)

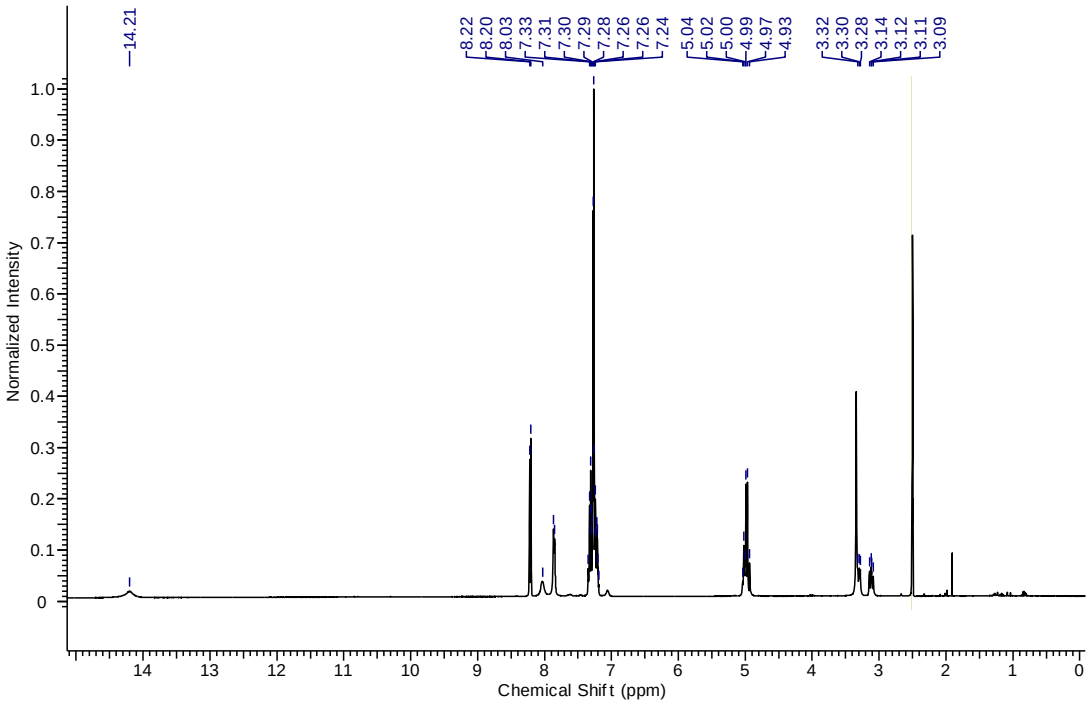


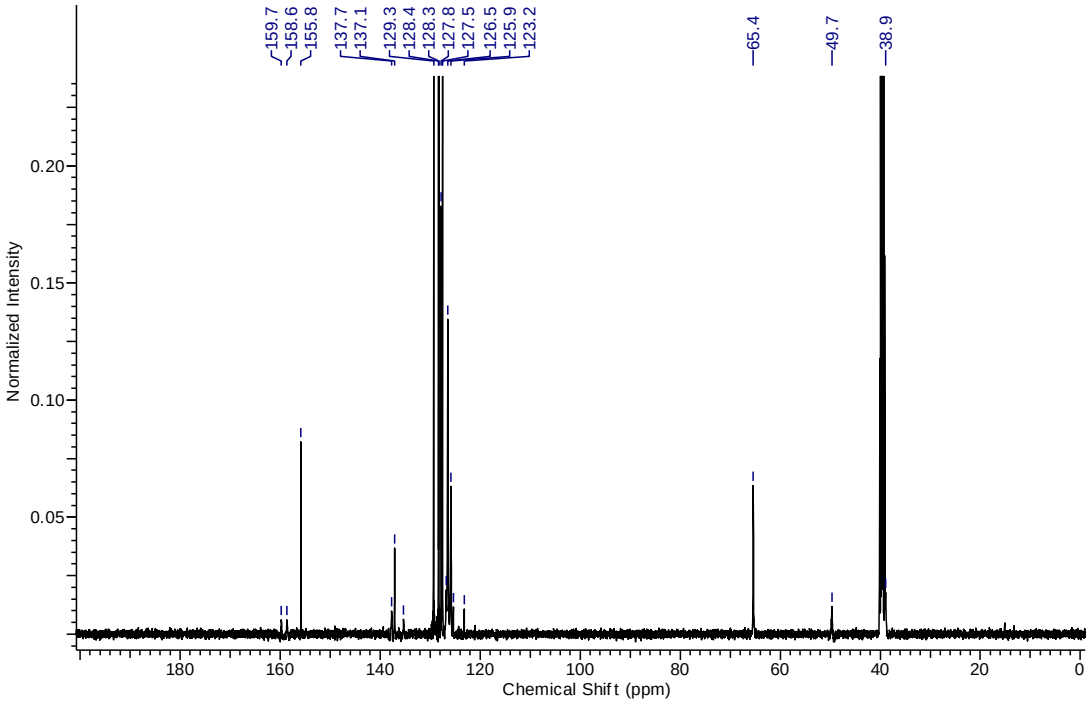




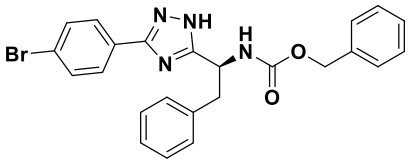
Benzyl (S)-(2-phenyl-1-(3-(4-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-5-yl)ethyl)carbamate (103)

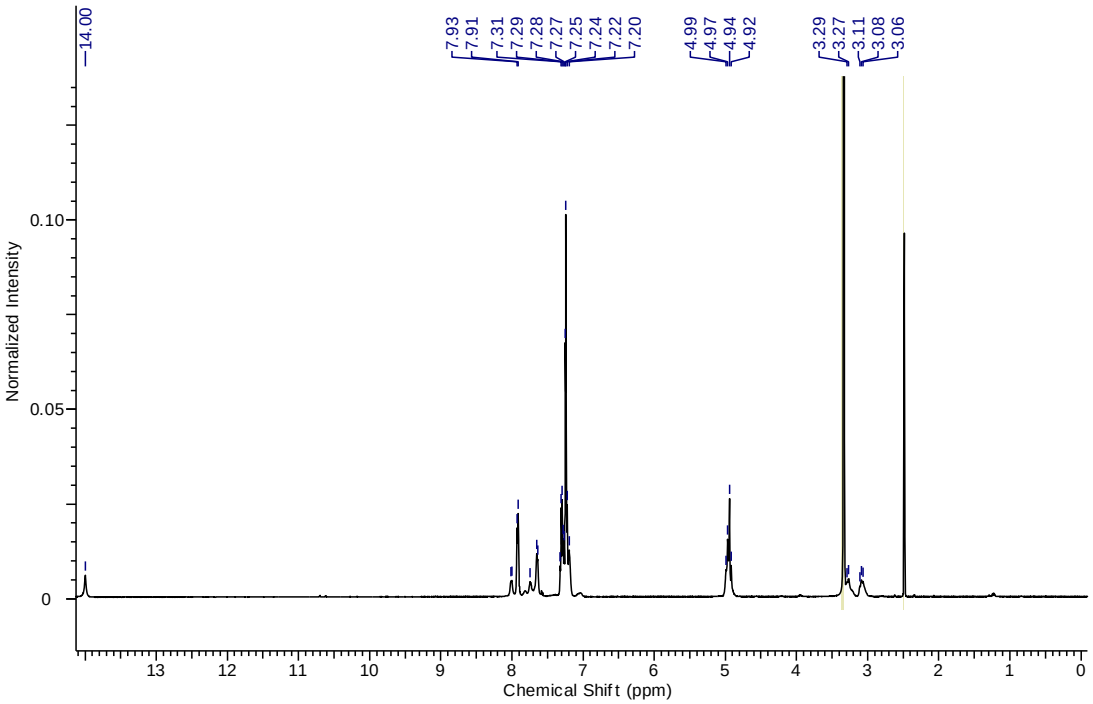


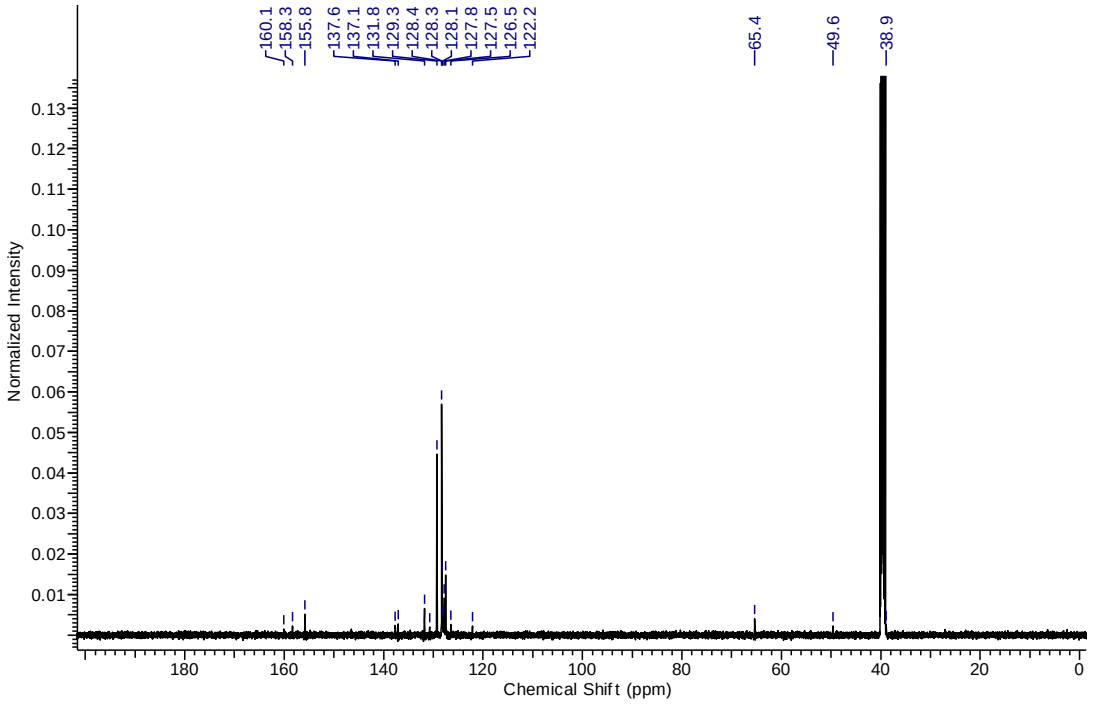




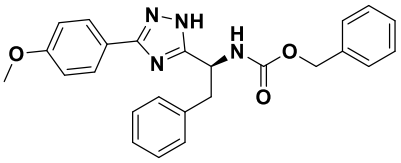
Benzyl (S)-(1-(3-(4-bromophenyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (104)

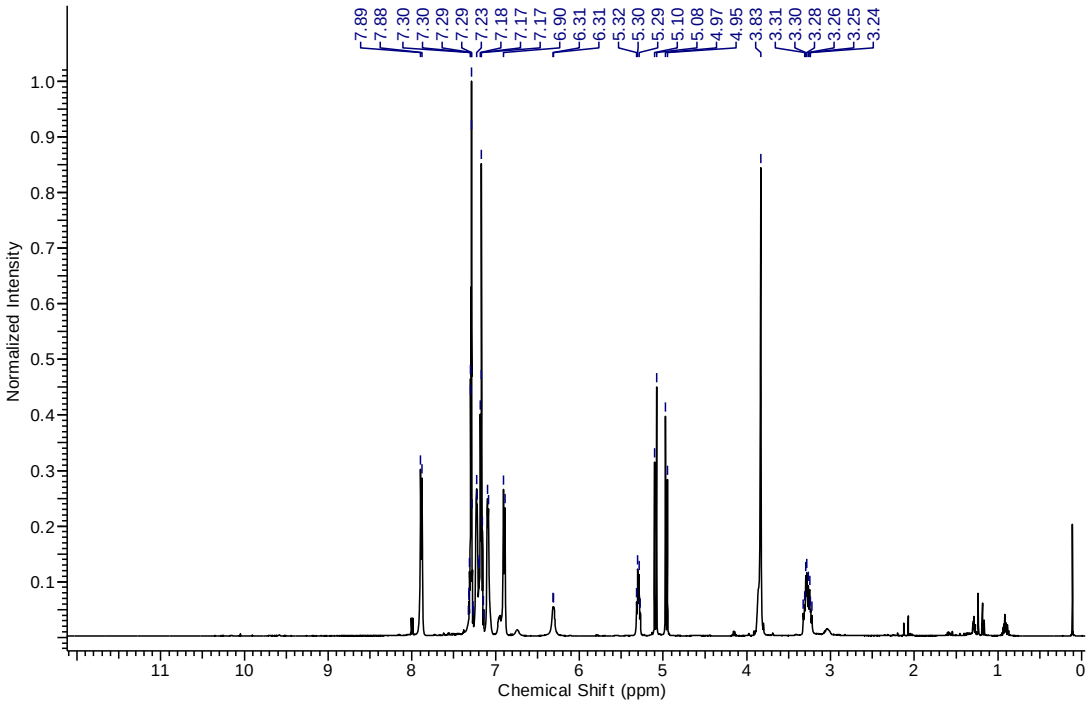


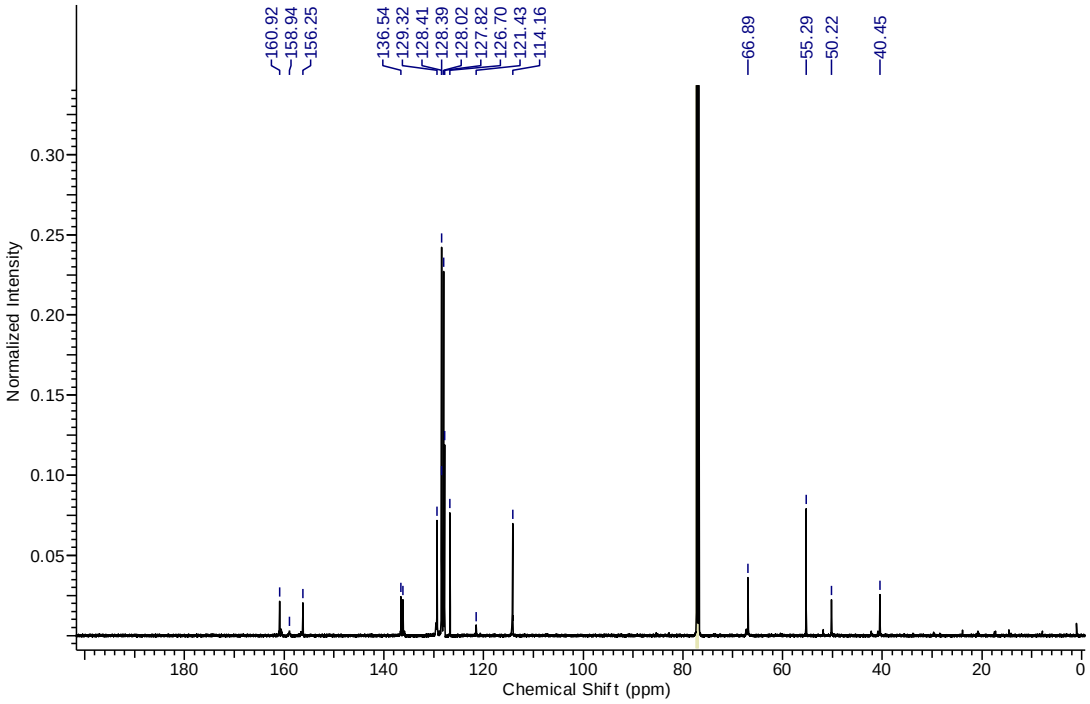




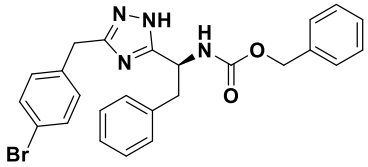
Benzyl (S)-(1-(3-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (105)

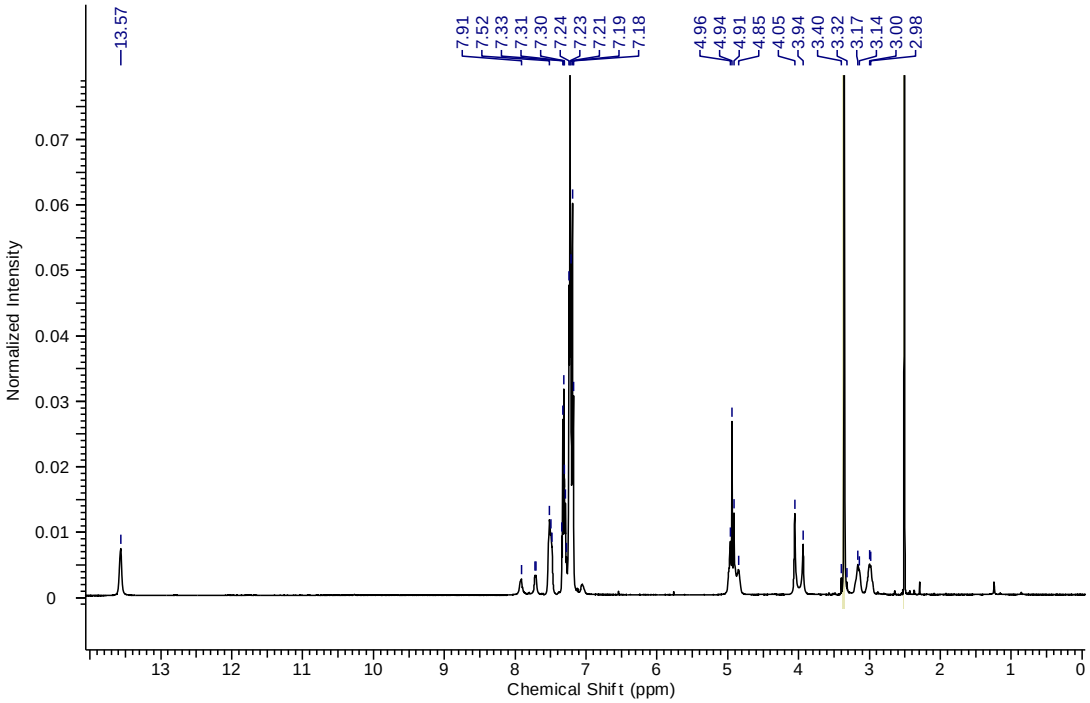


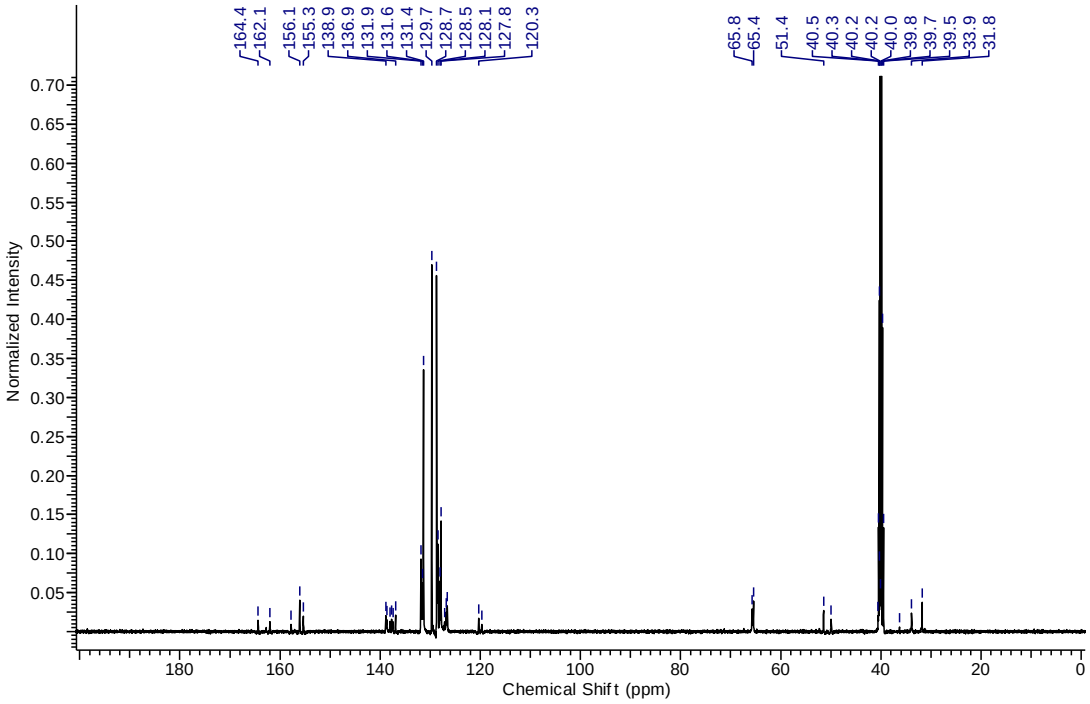




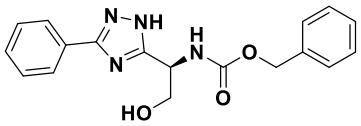
Benzyl (S)-(1-(3-(4-bromobenzyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (106)

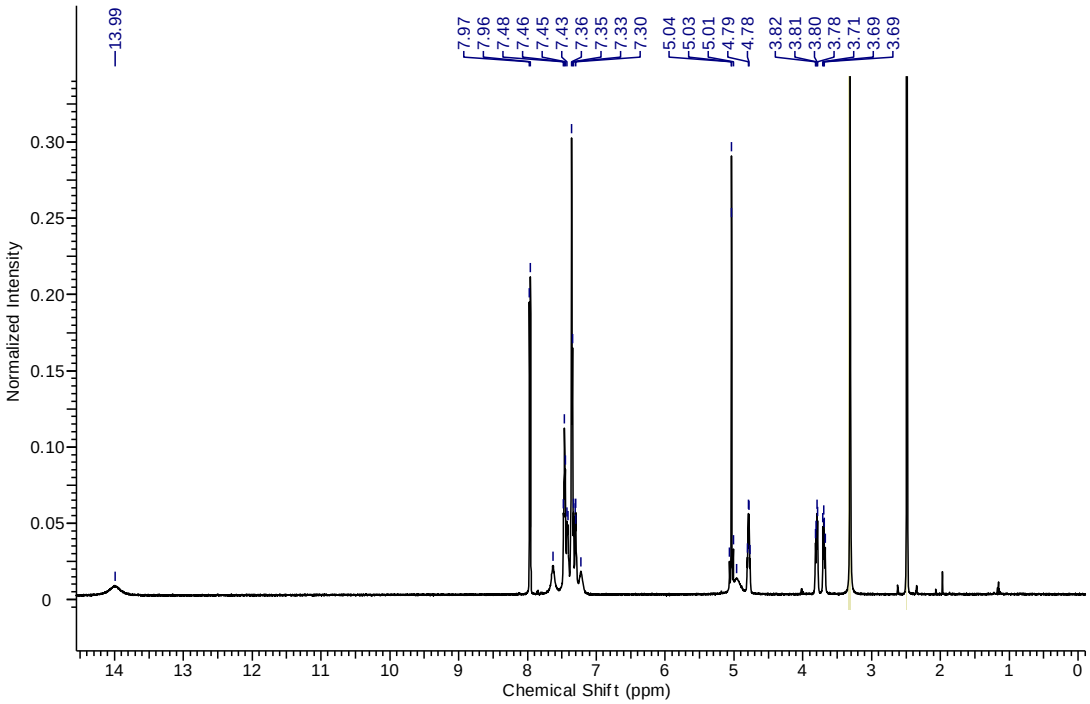


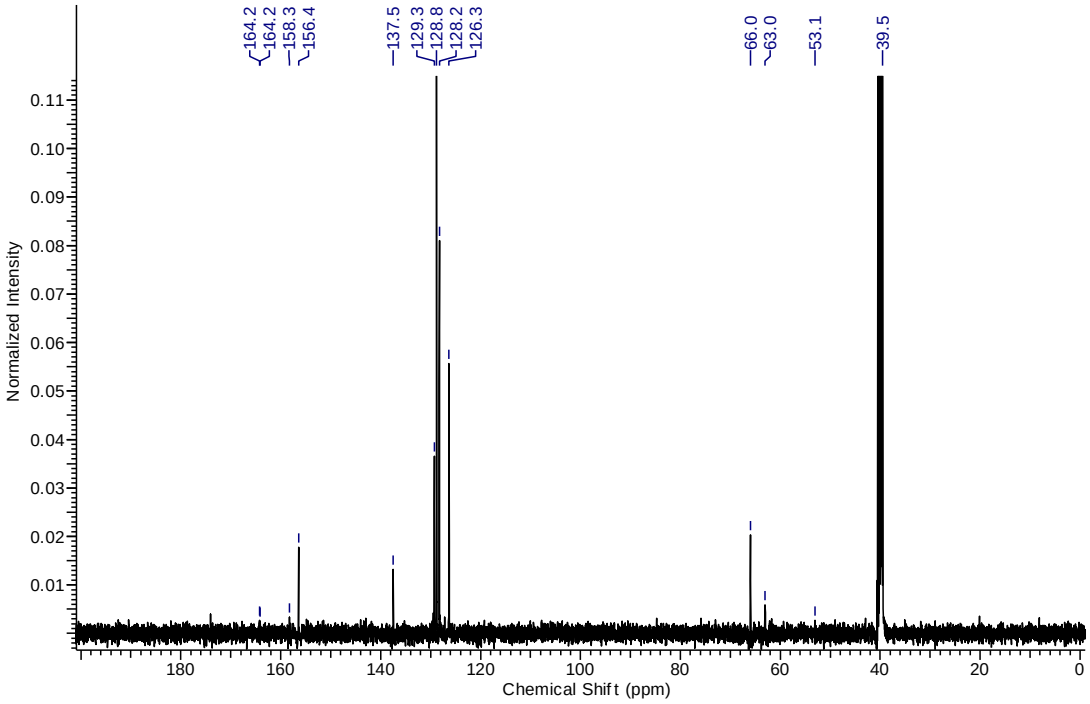




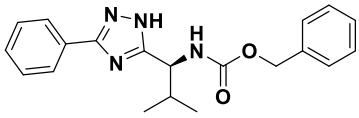
Benzyl (S)-(2-hydroxy-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate (107)

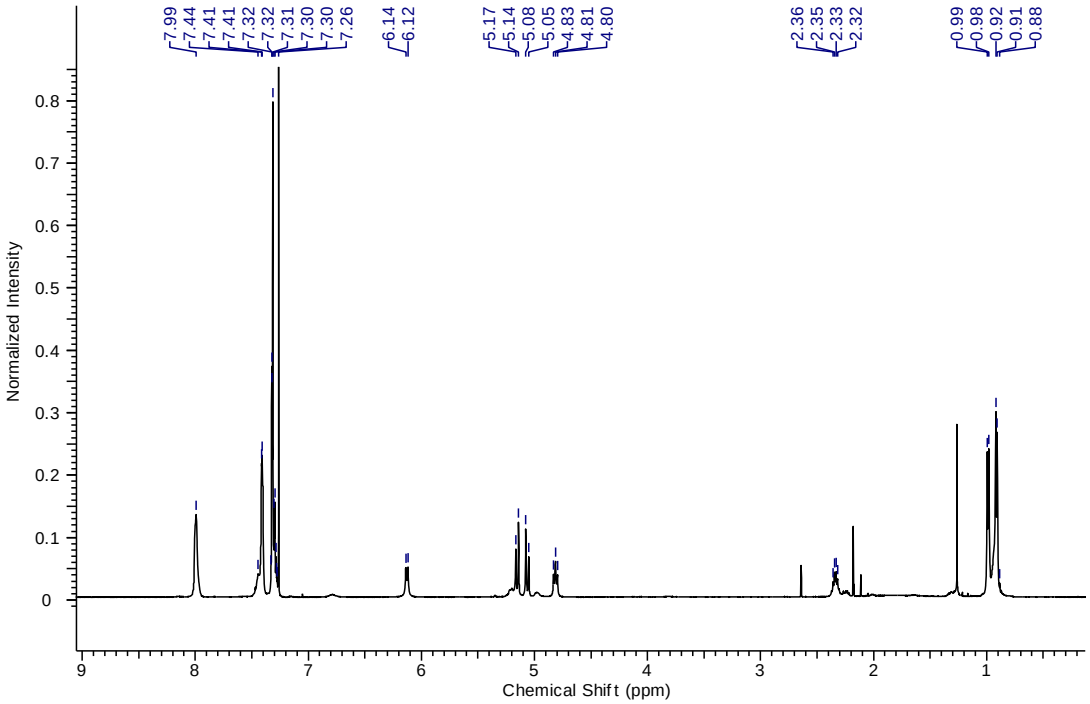


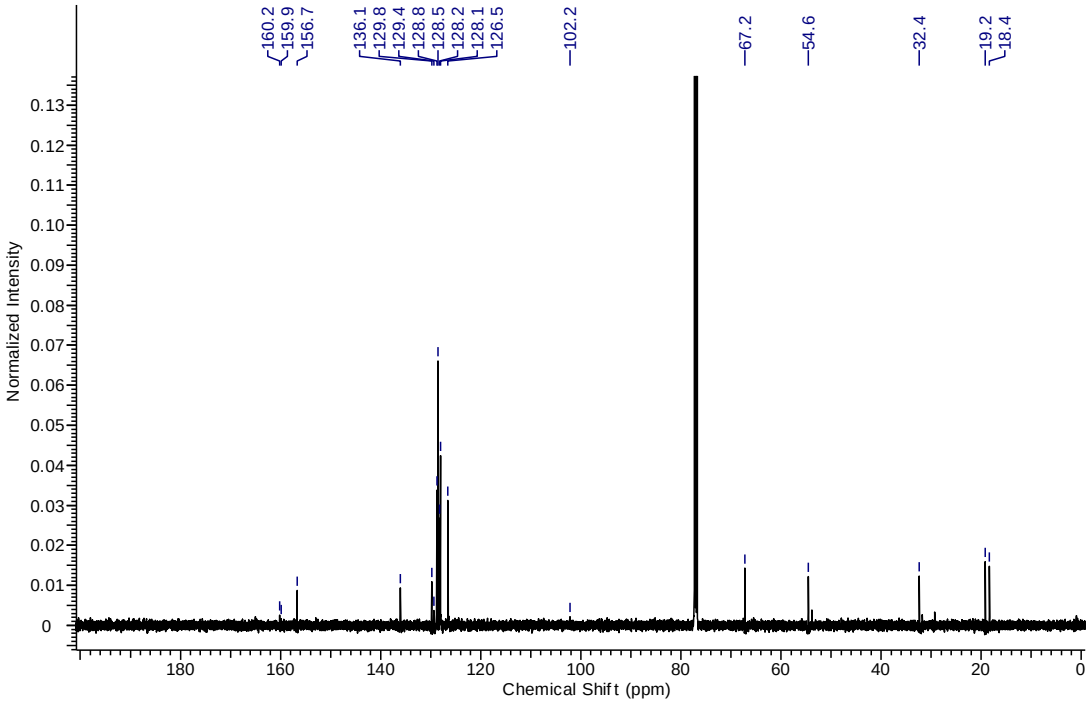




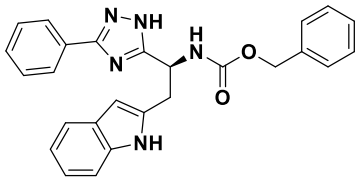
Benzyl (S)-(2-methyl-1-(3-phenyl-1H-1,2,4-triazol-5-yl)propyl)carbamate (108)

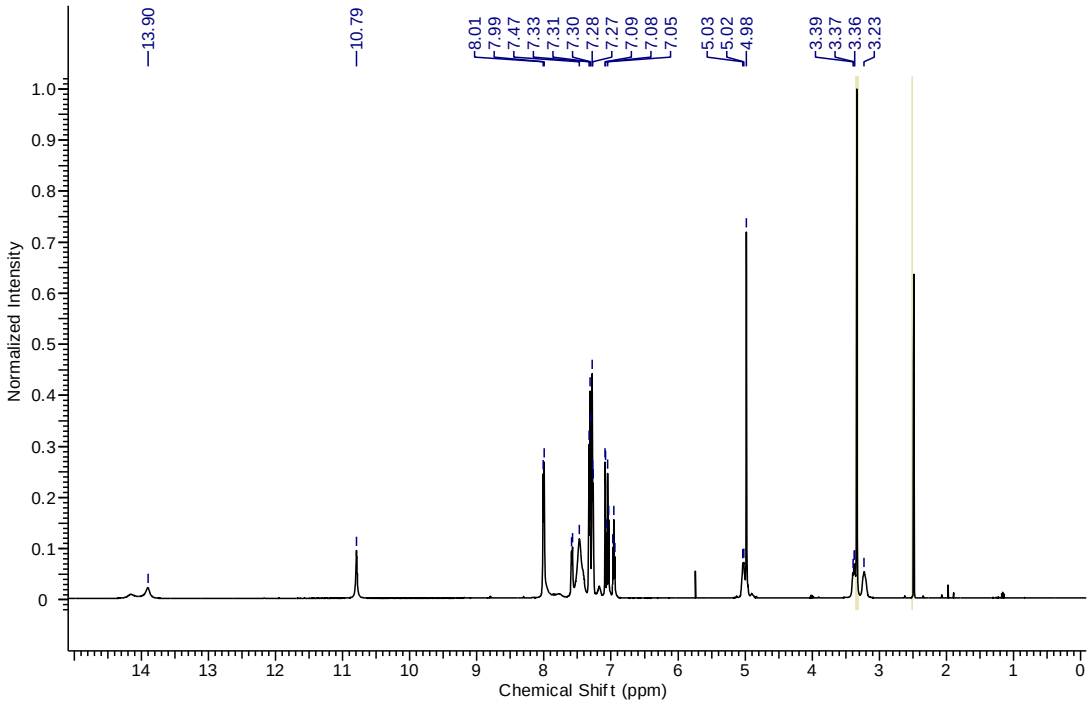


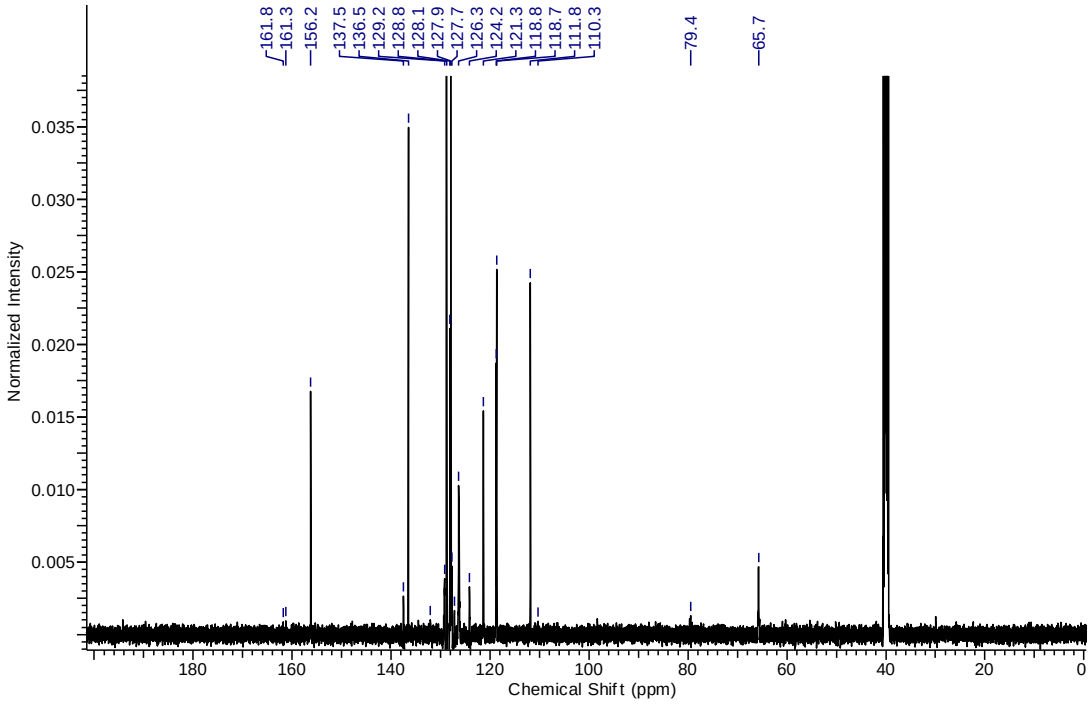




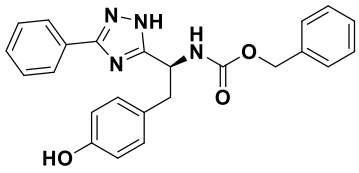
Benzyl (S)-(2-(1H-indol-3-yl)-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate (109)

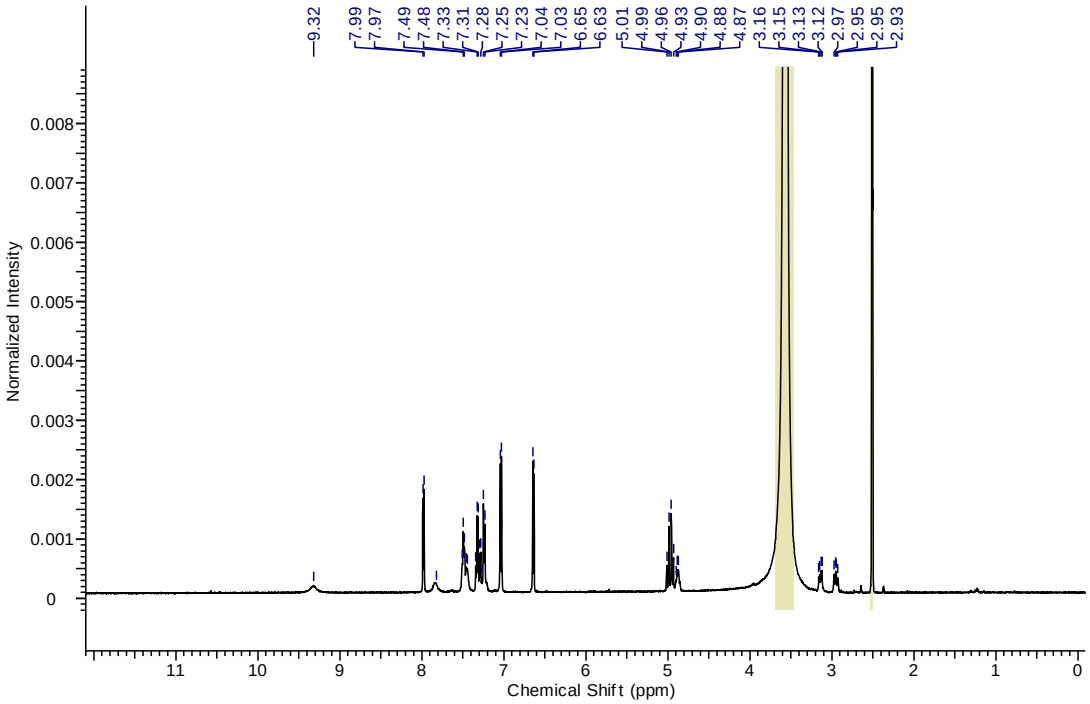


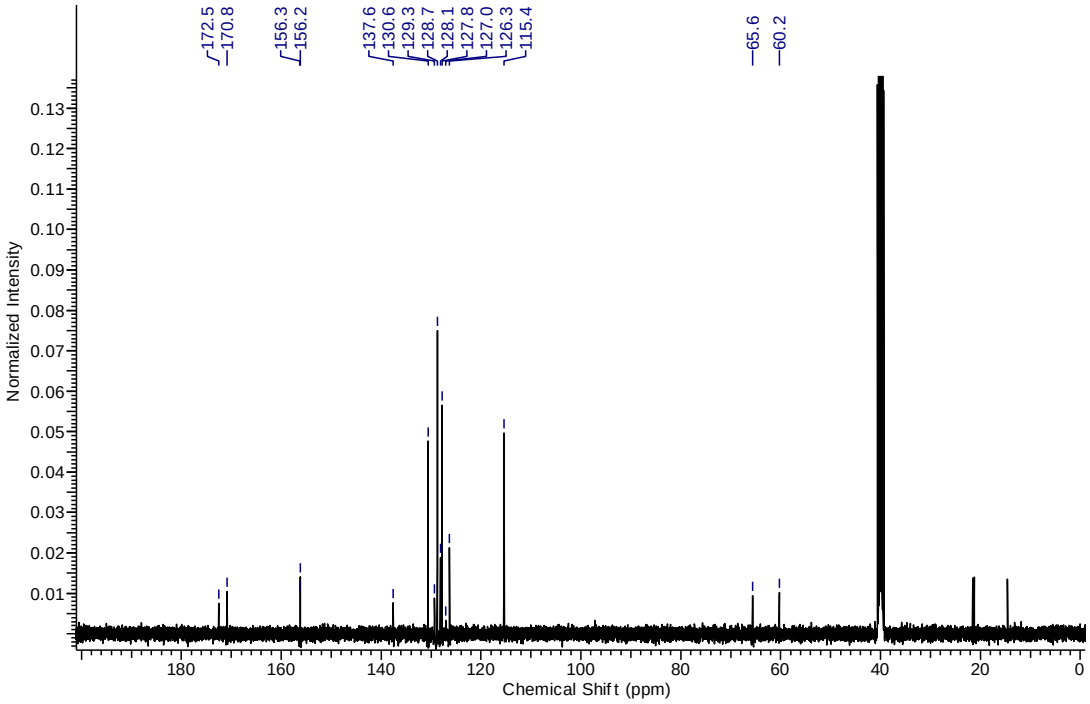




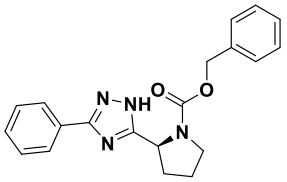
Benzyl (S)-(2-(4-hydroxyphenyl)-1-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate (110)

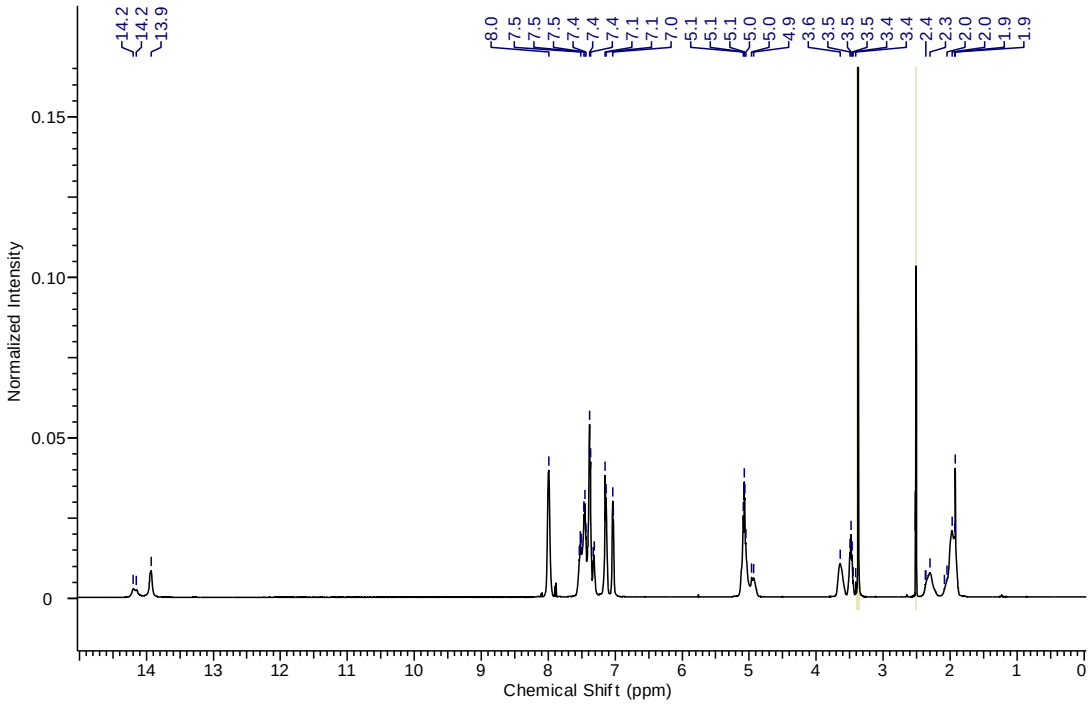


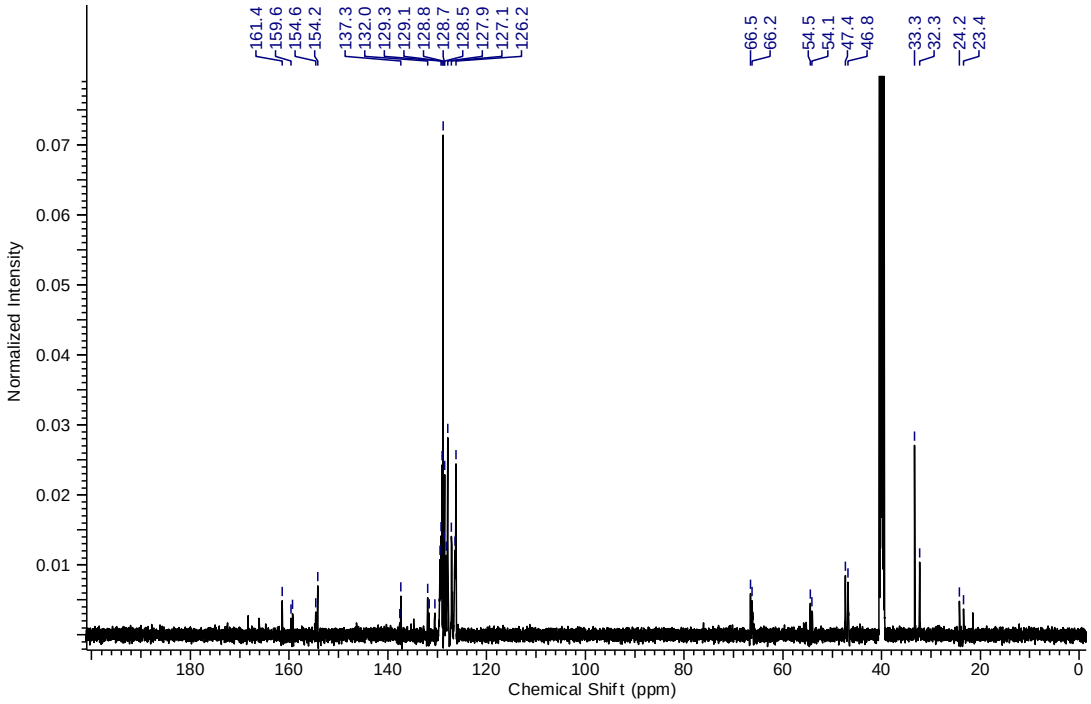




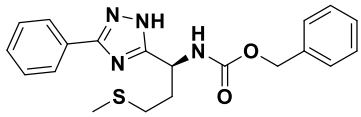
Benzyl (S)-2-(3-phenyl-1H-1,2,4-triazol-5-yl)pyrrolidine-1-carboxylate (111)

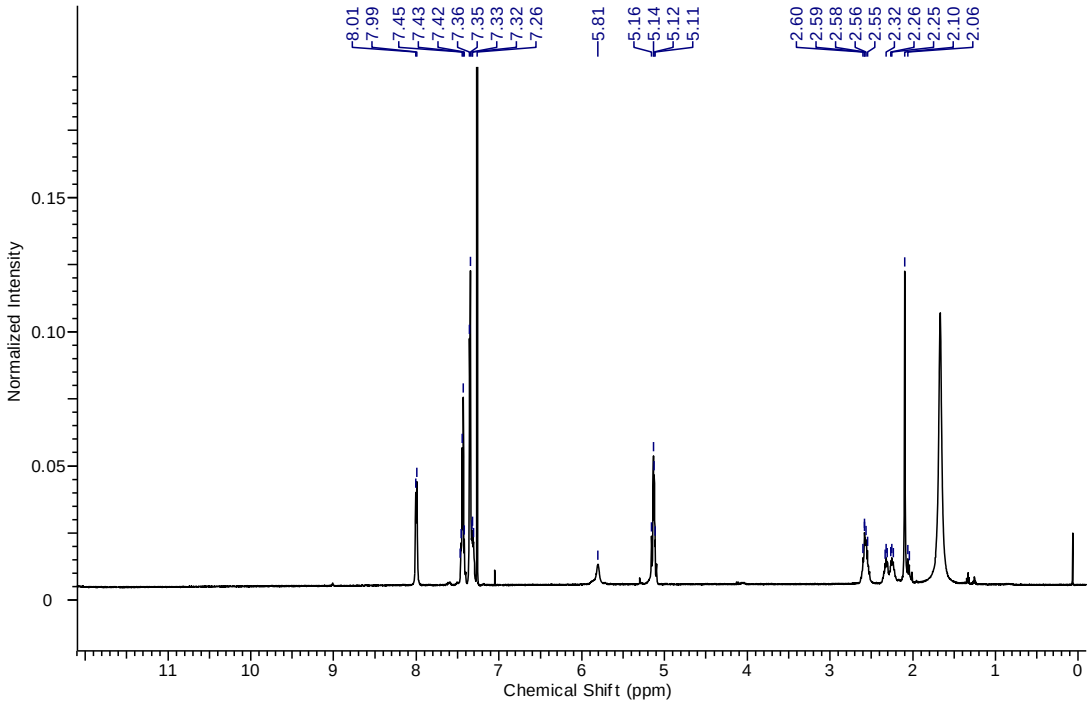


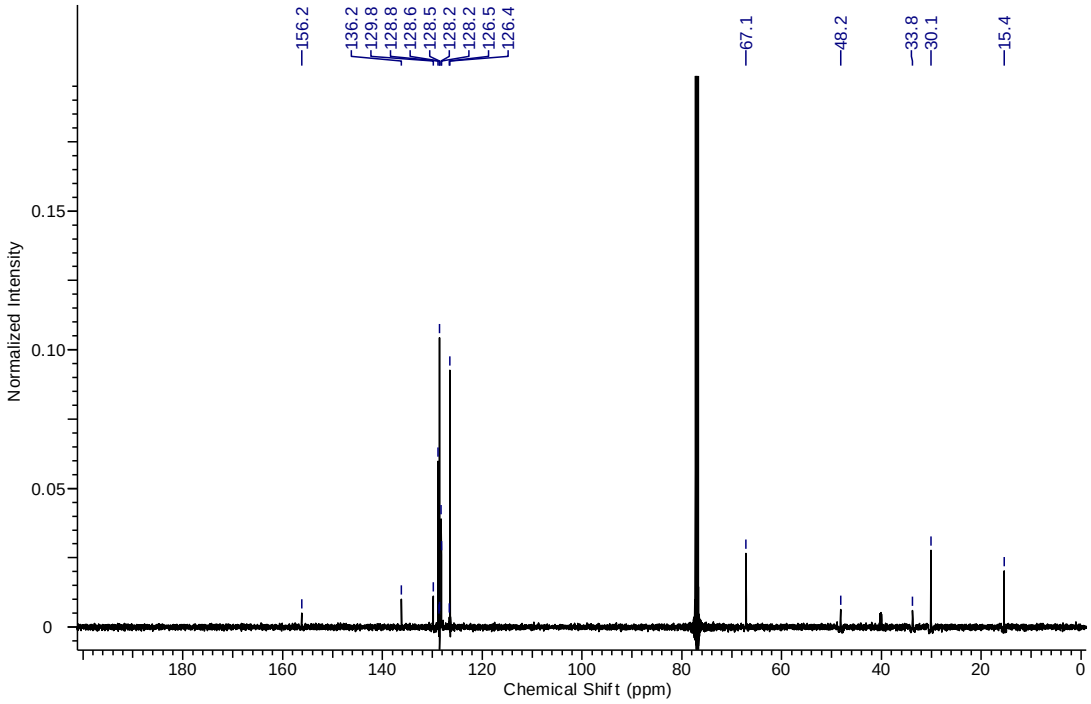




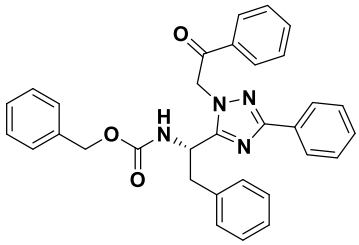
Benzyl (S)-(3-(methylthio)-1-(3-phenyl-1H-1,2,4-triazol-5-yl)propyl)carbamate (112)

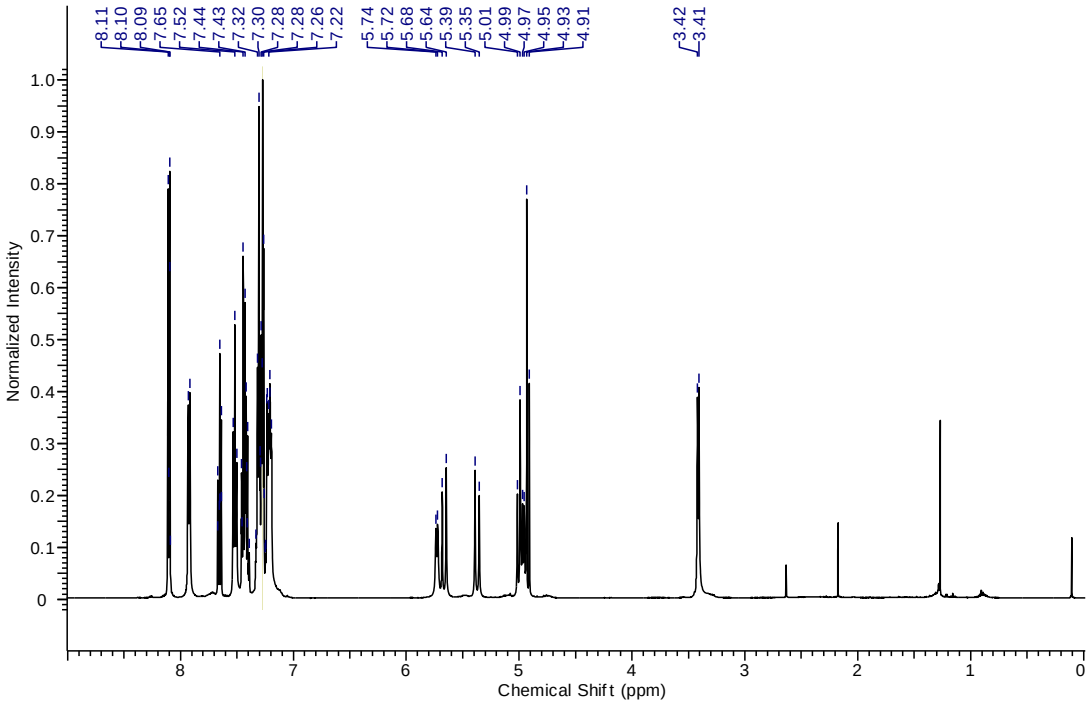


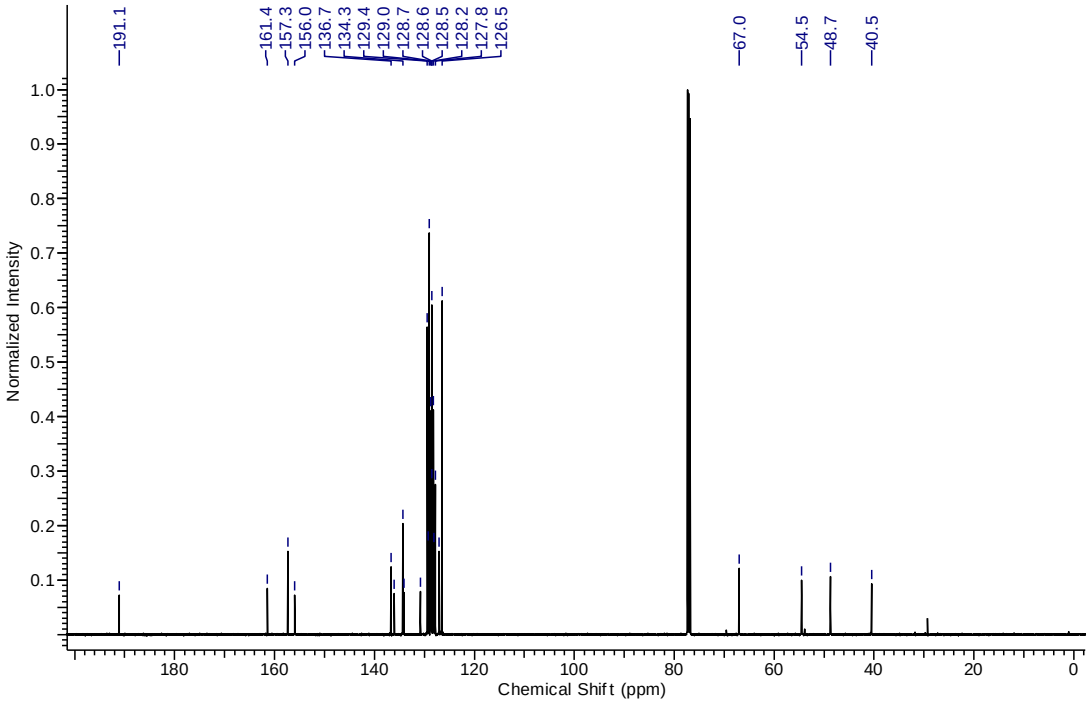




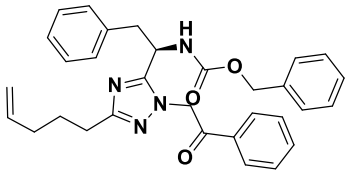
Benzyl ((1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)methyl)carbamate (56)

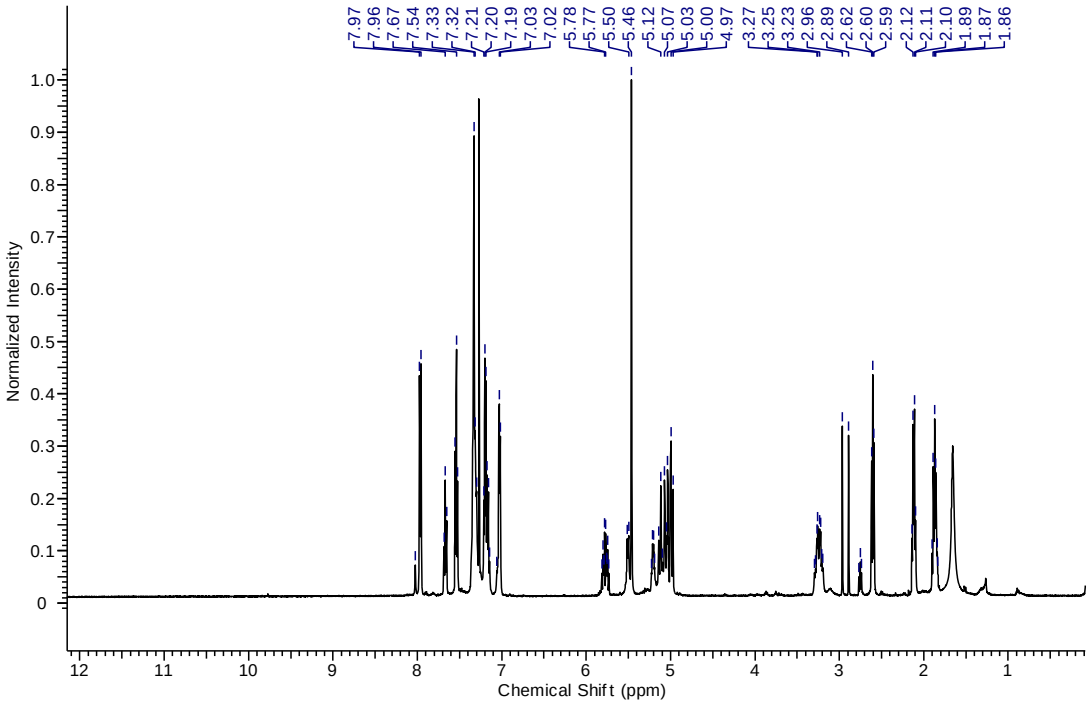


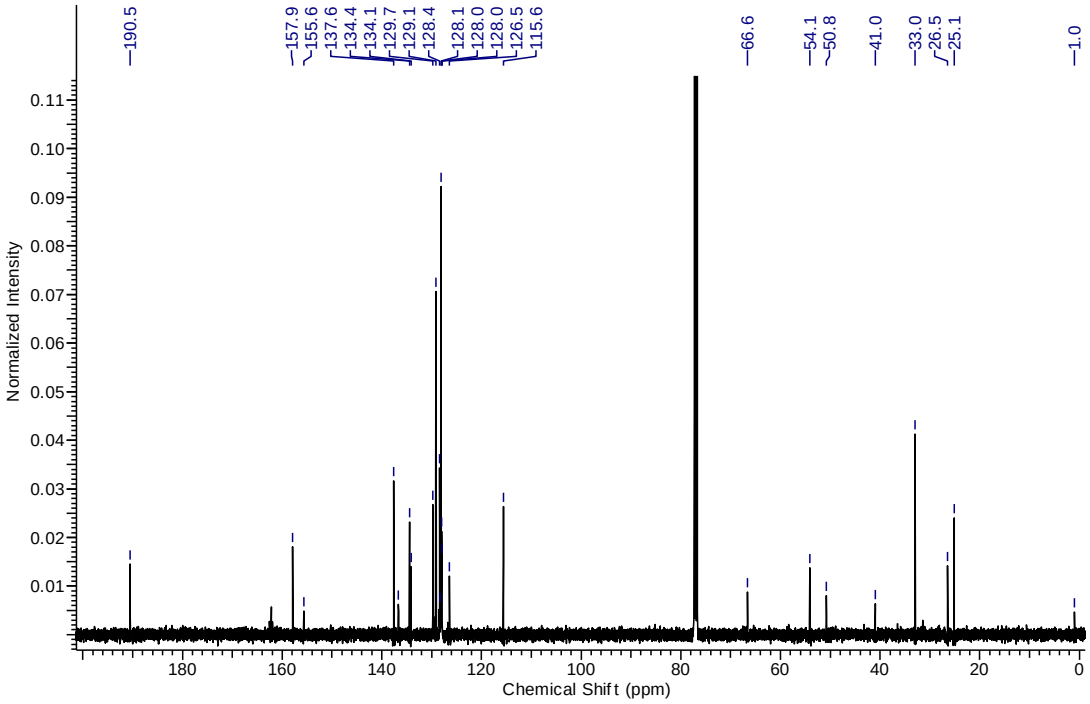




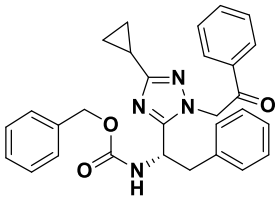
Benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-3-(pent-4-en-1-yl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (119)

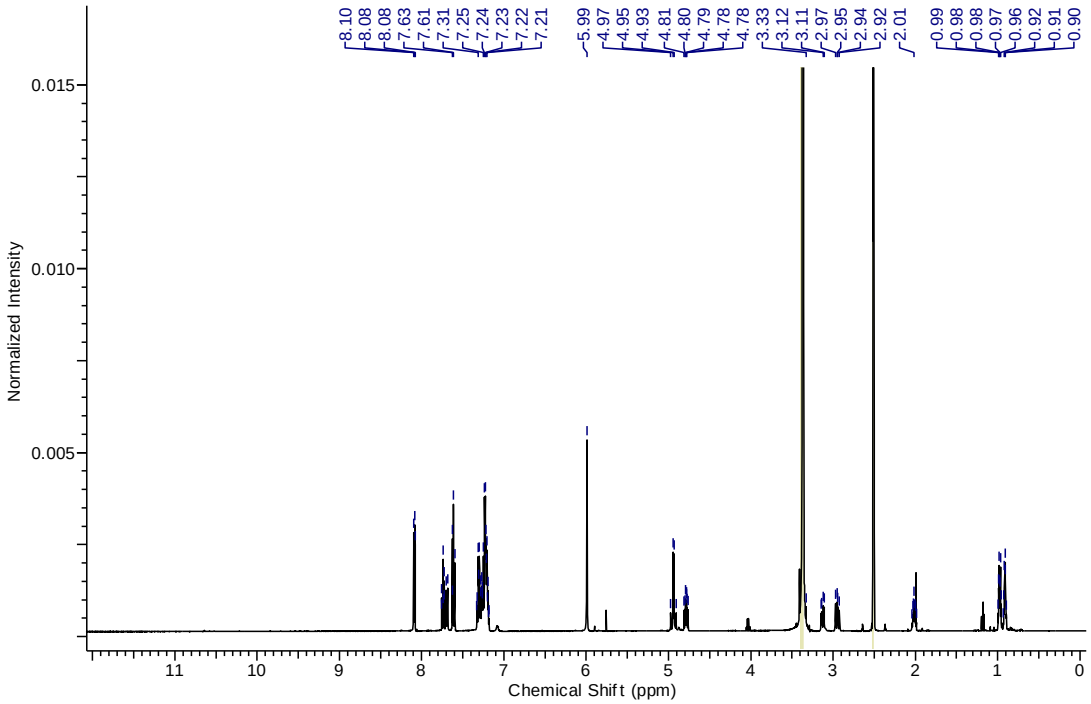


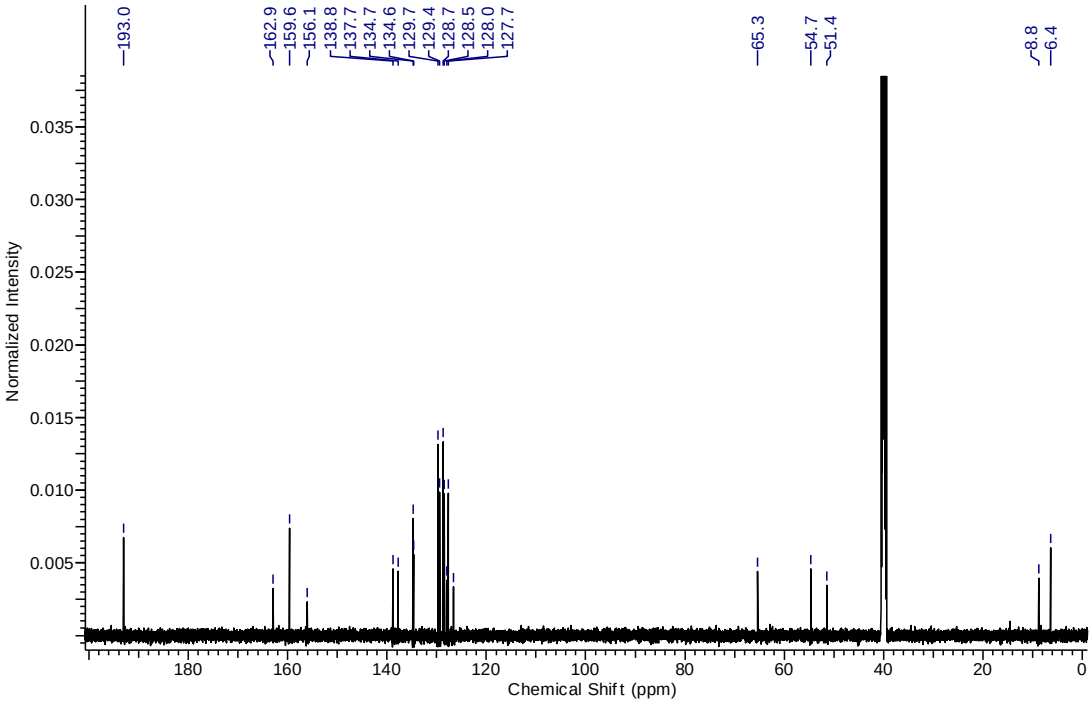




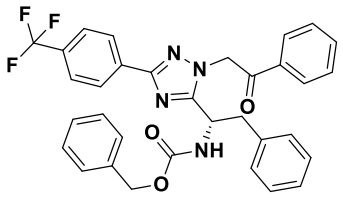
(S)-Benzyl 1-(3-cyclopropyl-1-(2-oxo-2-phenylethyl)-1H-1,2,4-triazol-5-yl)-2-phenylethylcarbamate (120)

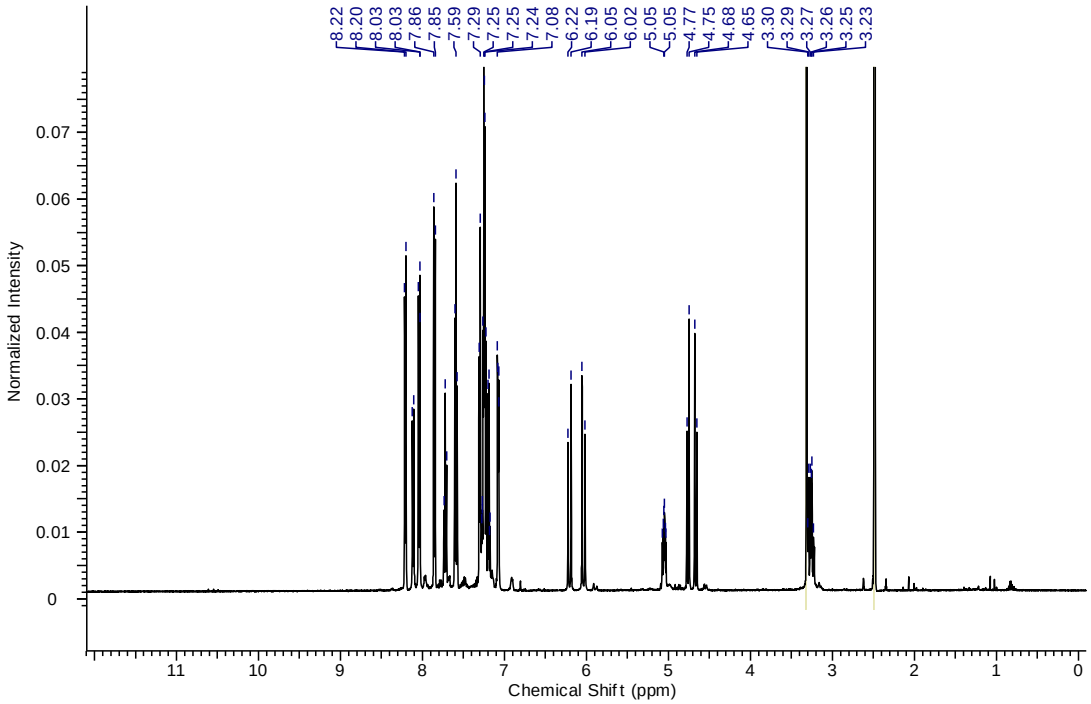


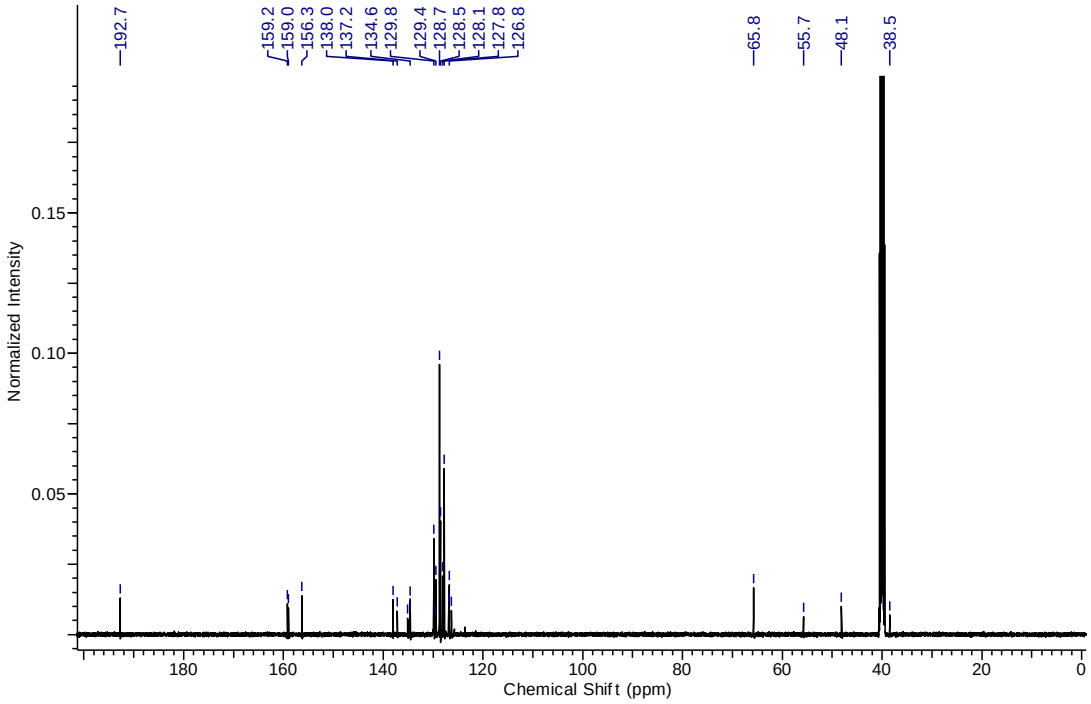




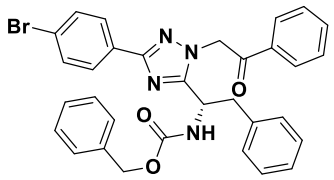
Benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-3-(4-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (121)

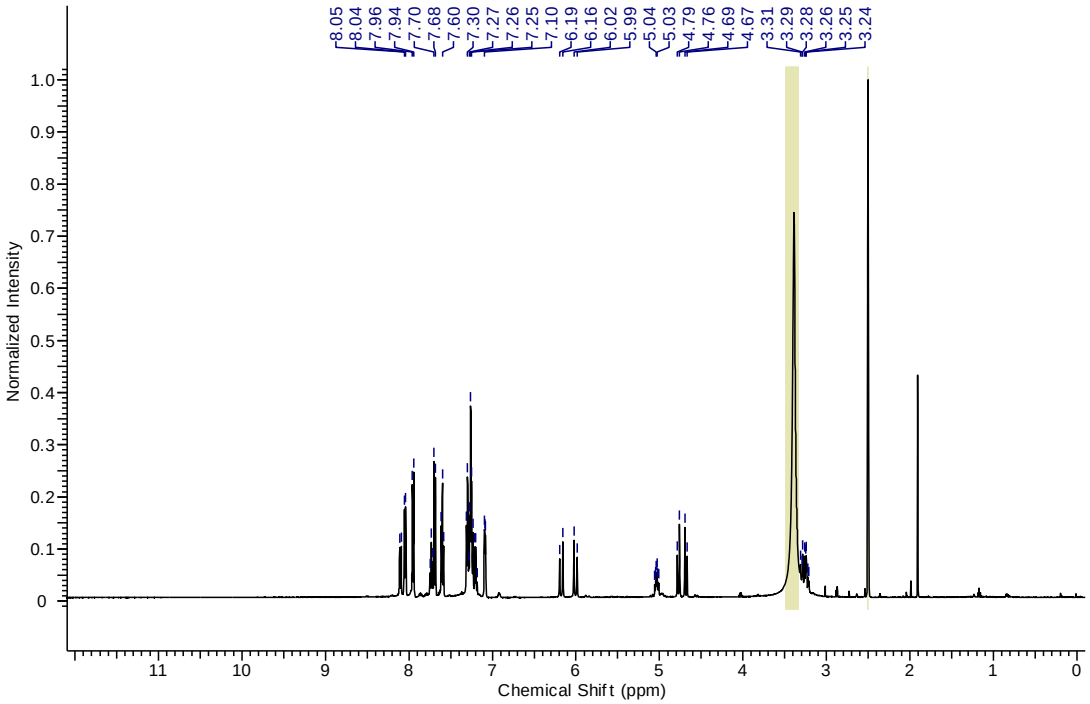


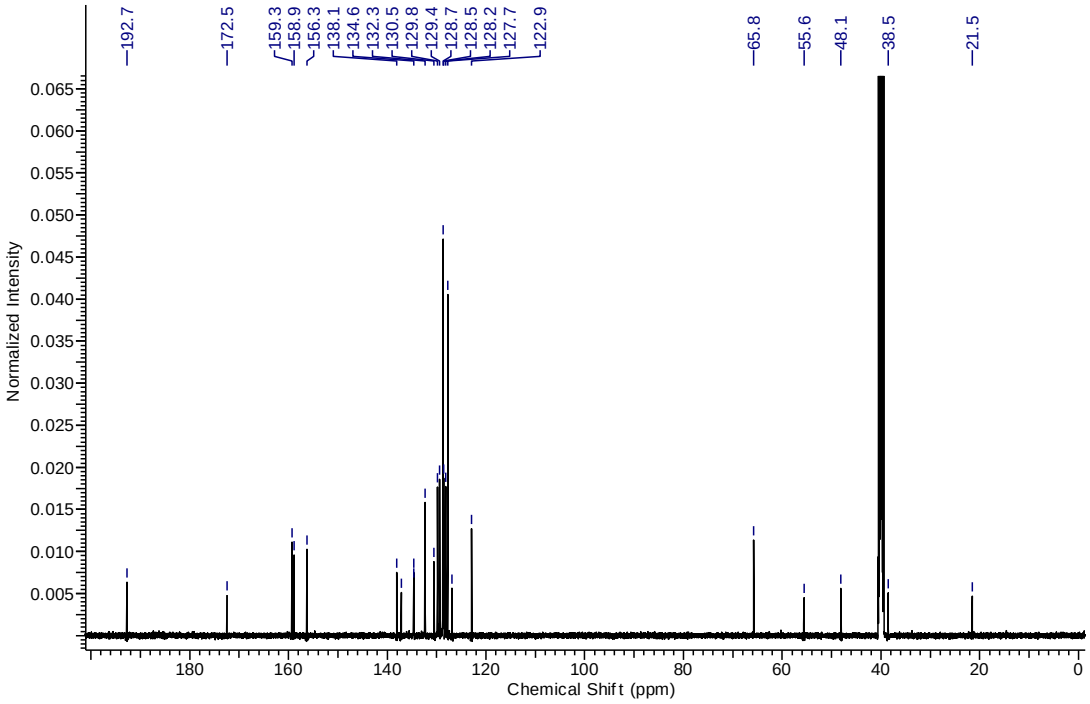




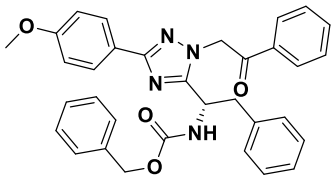
Benzyl (S)-(1-(3-(4-bromophenyl)-1-(2-oxo-2-phenylethyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (122)

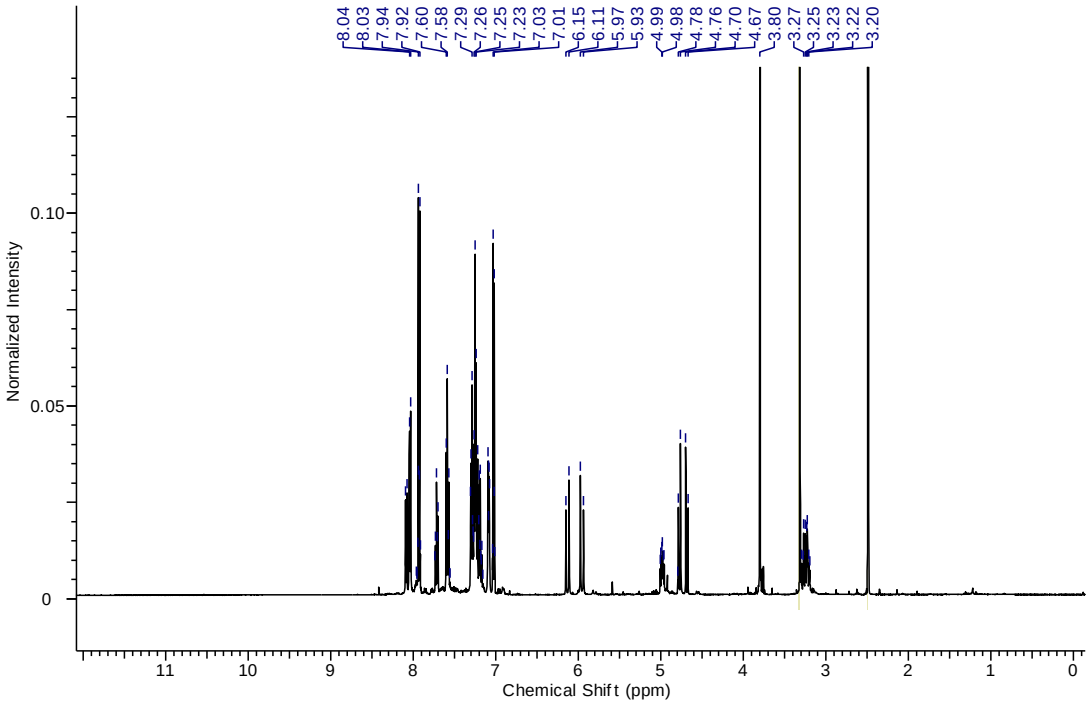


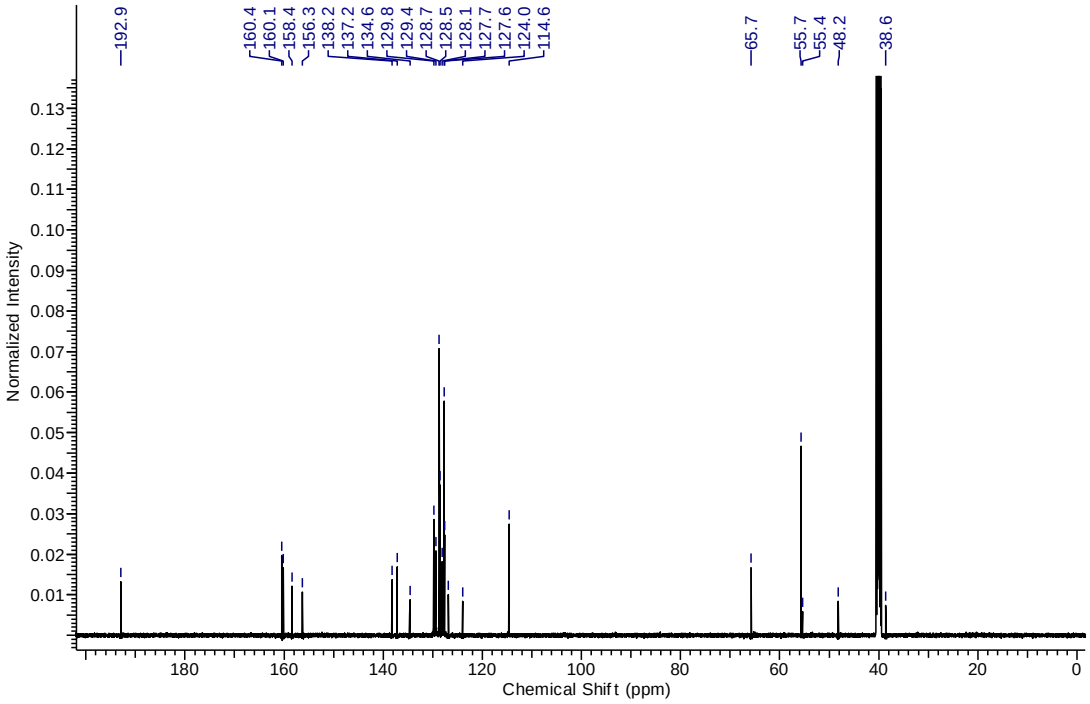




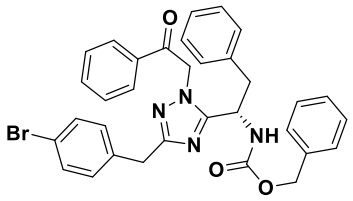
Benzyl (S)-(1-(3-(4-methoxyphenyl)-1-(2-oxo-2-phenylethyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (123)

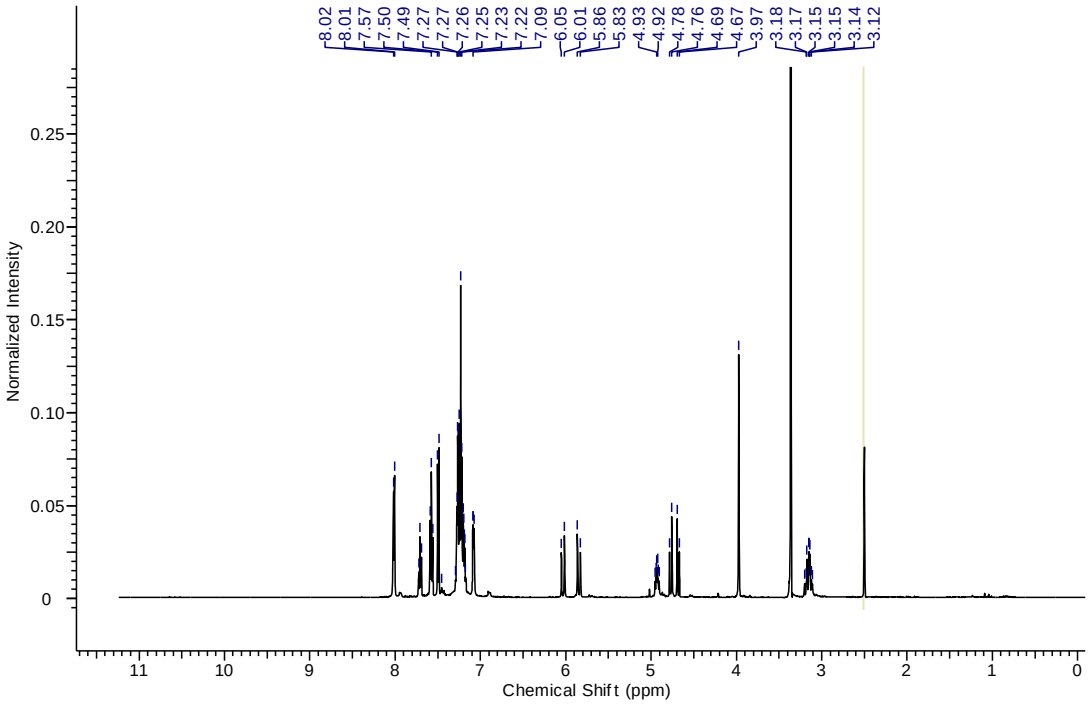


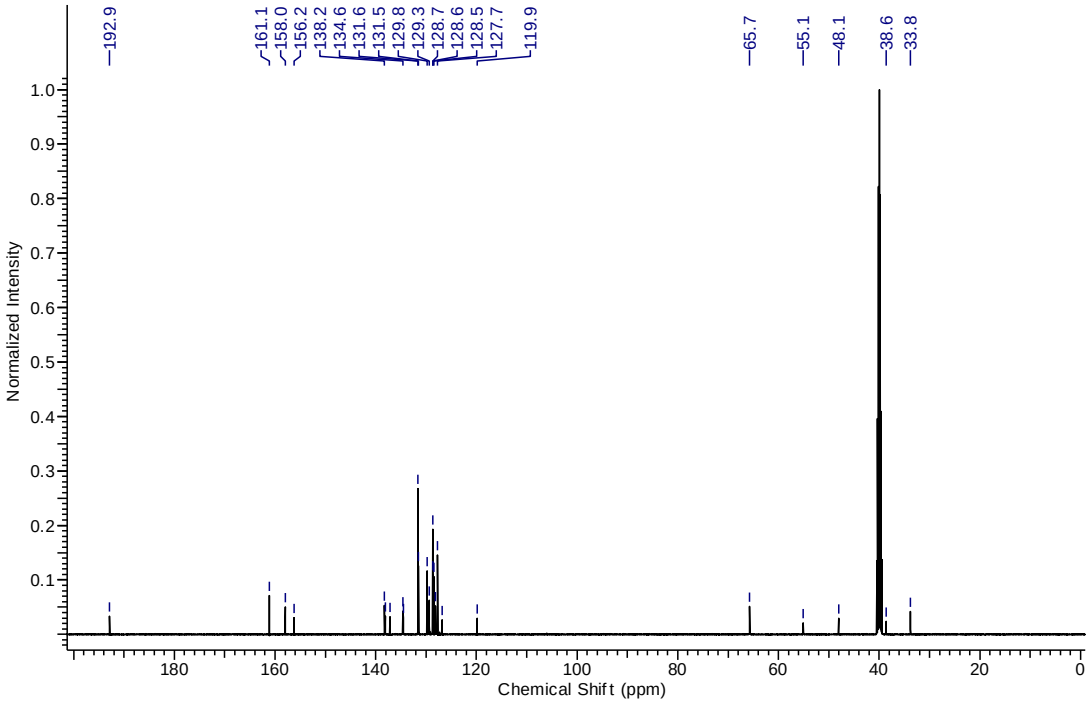




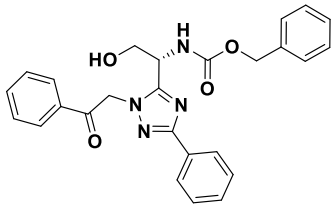
Benzyl (S)-(1-(3-(4-bromobenzyl)-1-(2-oxo-2-phenylethyl)-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (124)

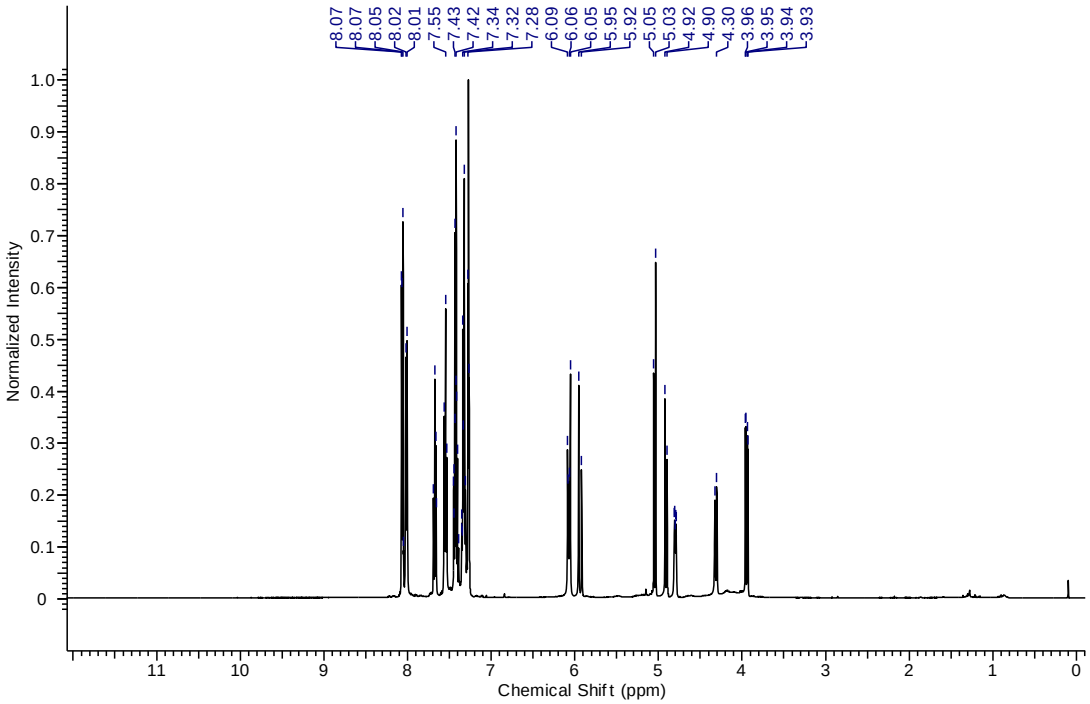


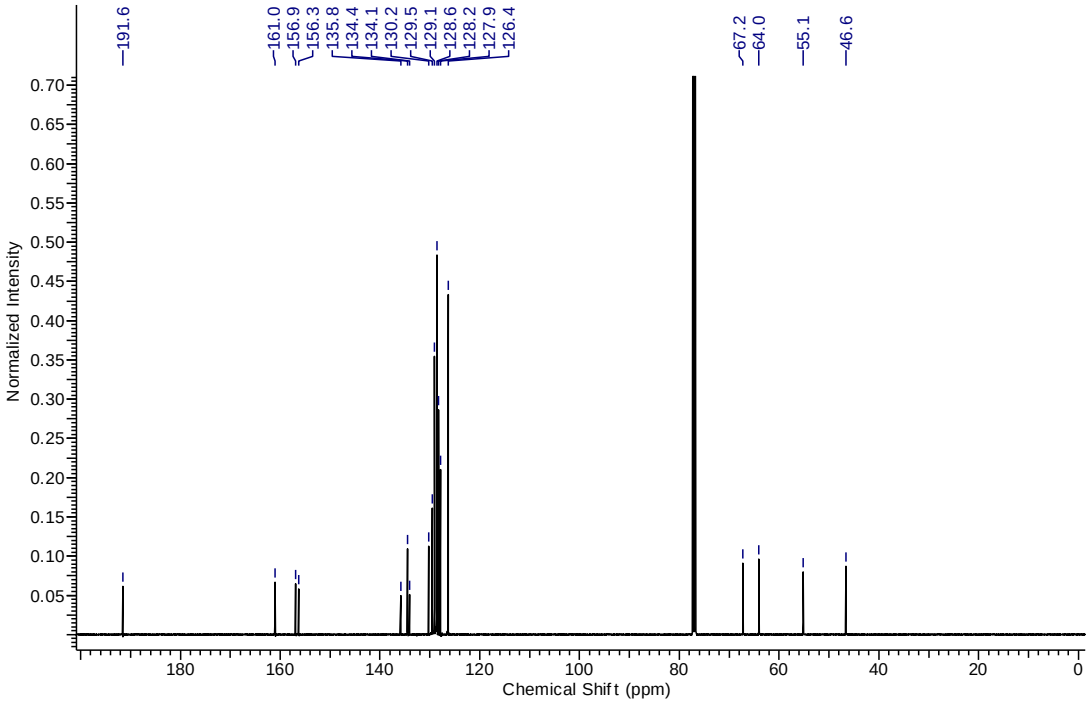




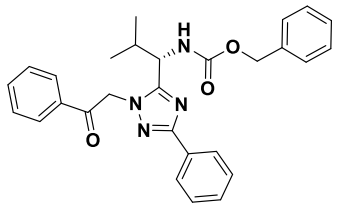
(S)-benzyl 2-hydroxy-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)ethylcarbamate (125)

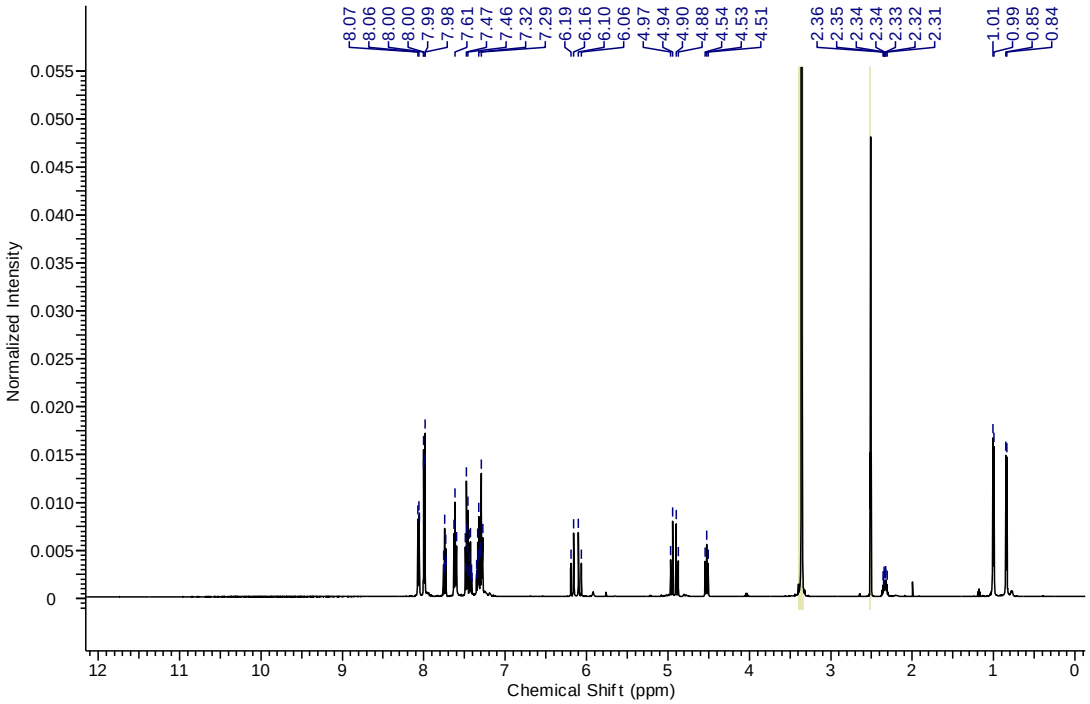


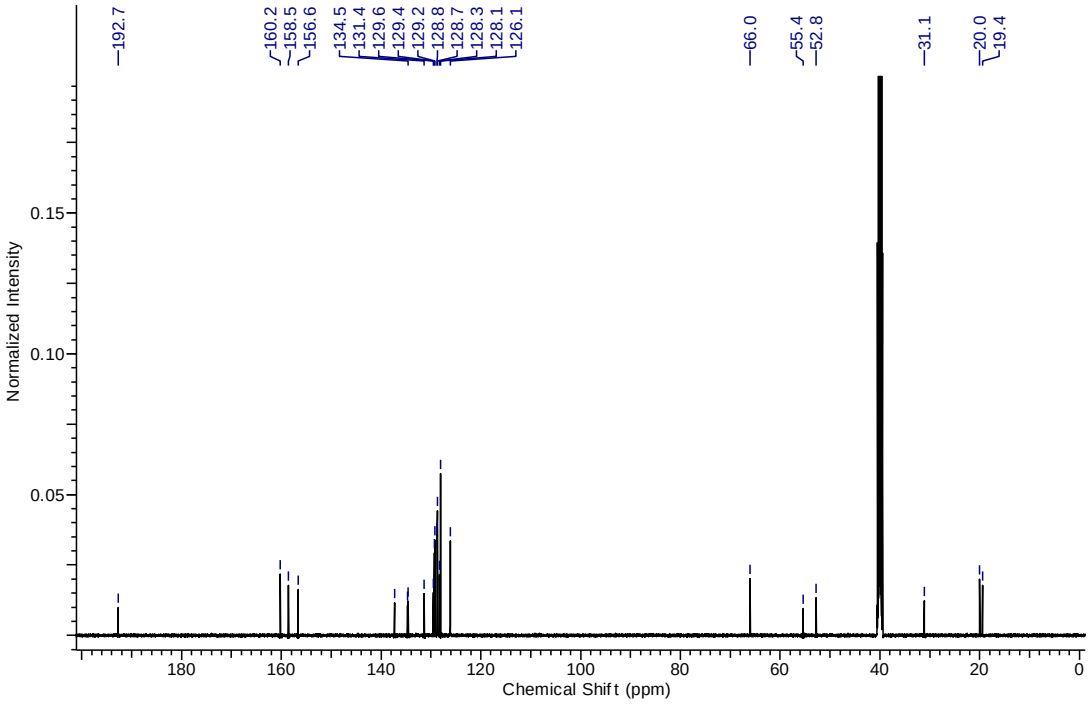




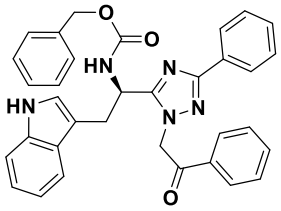
Benzyl (S)-(2-methyl-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)propyl)carbamate (126)

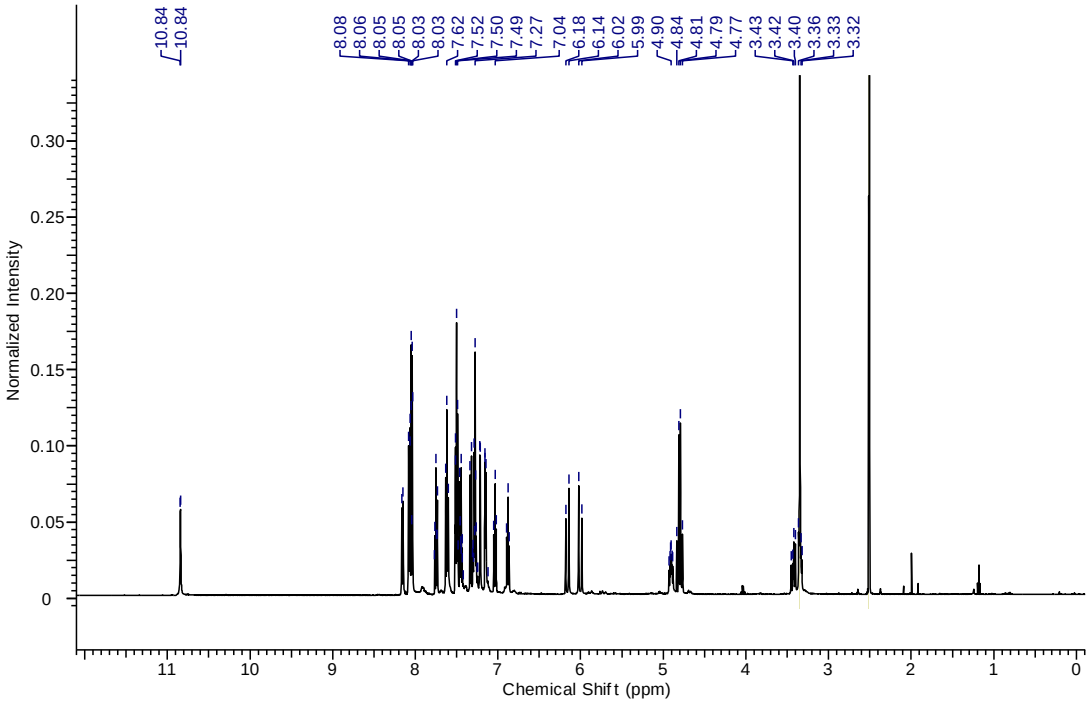


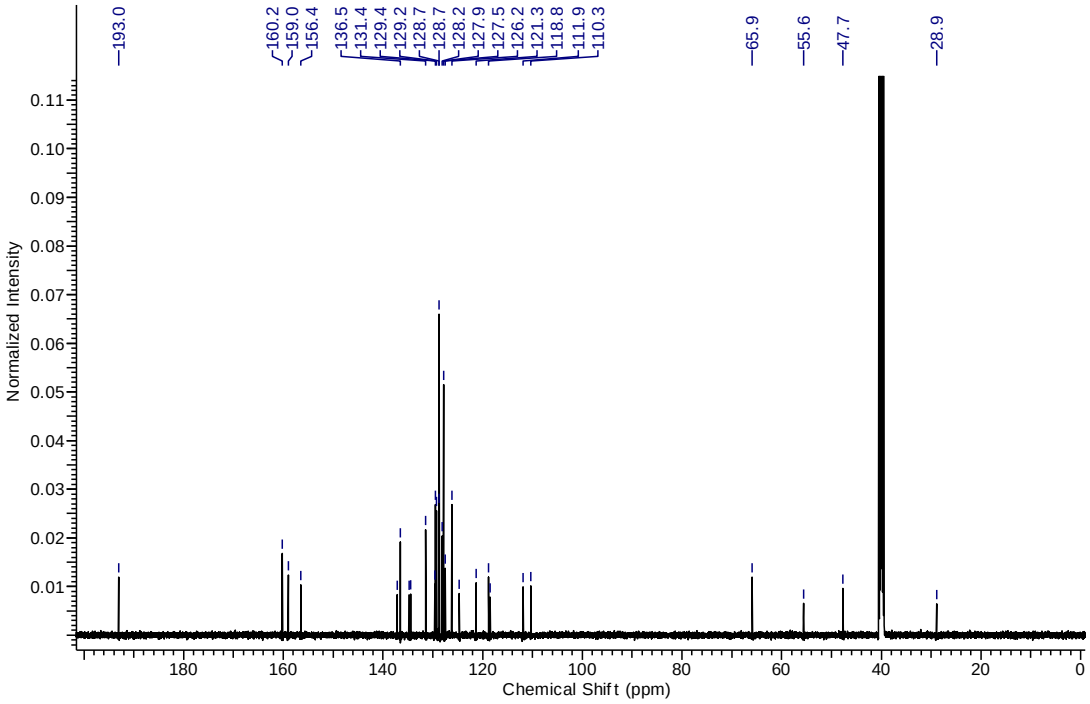




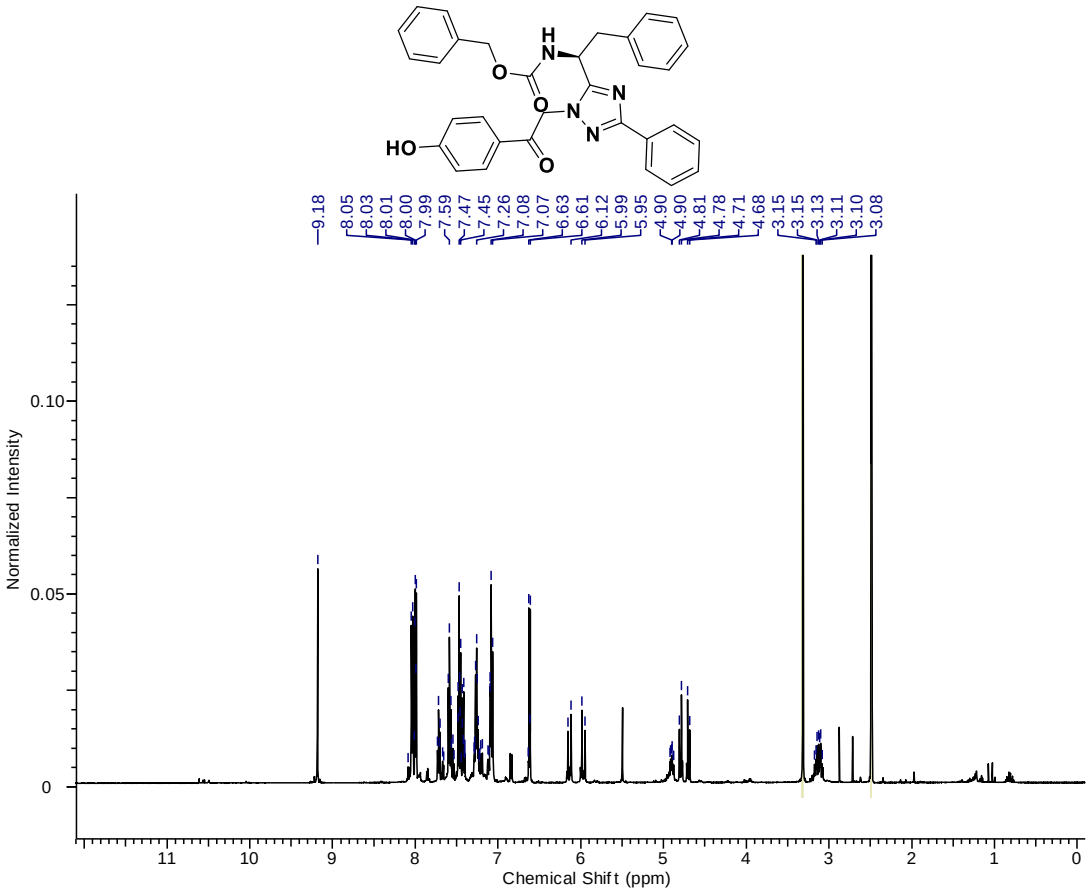
Benzyl (S)-(2-(1H-indol-3-yl)-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)carbamate (127)

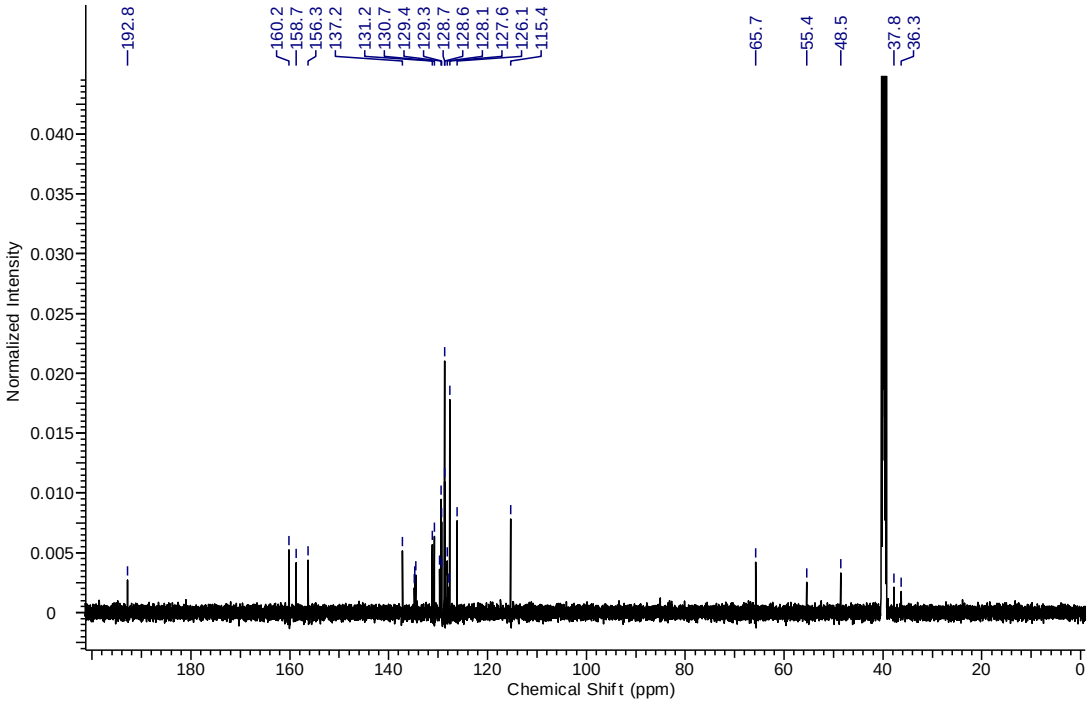




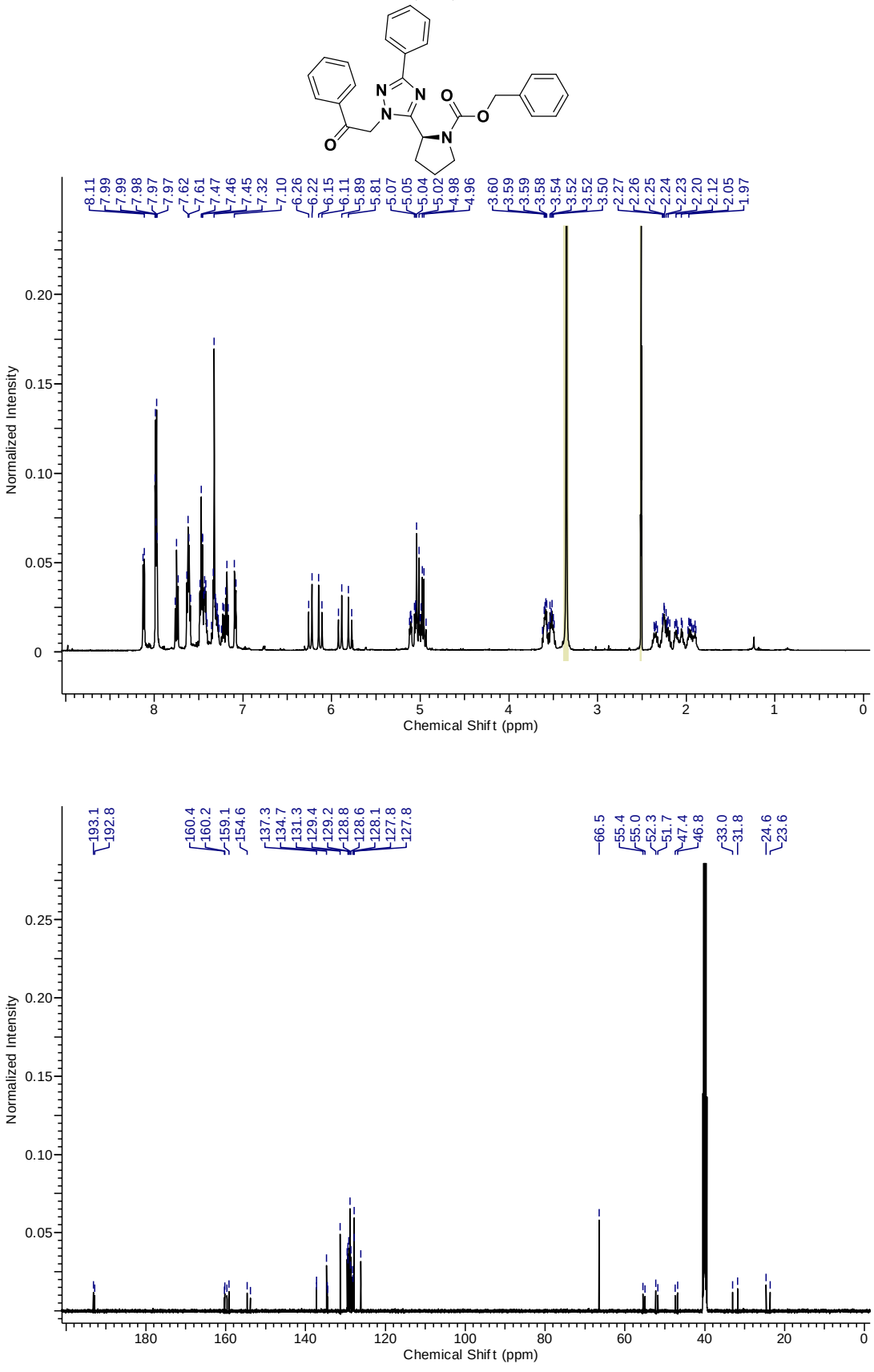


Benzyl (S)-(1-(1-(2-(4-hydroxyphenyl)-2-oxoethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (128)

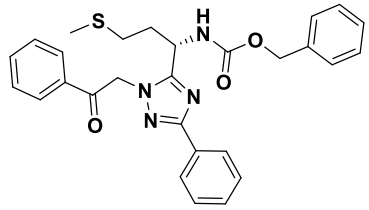


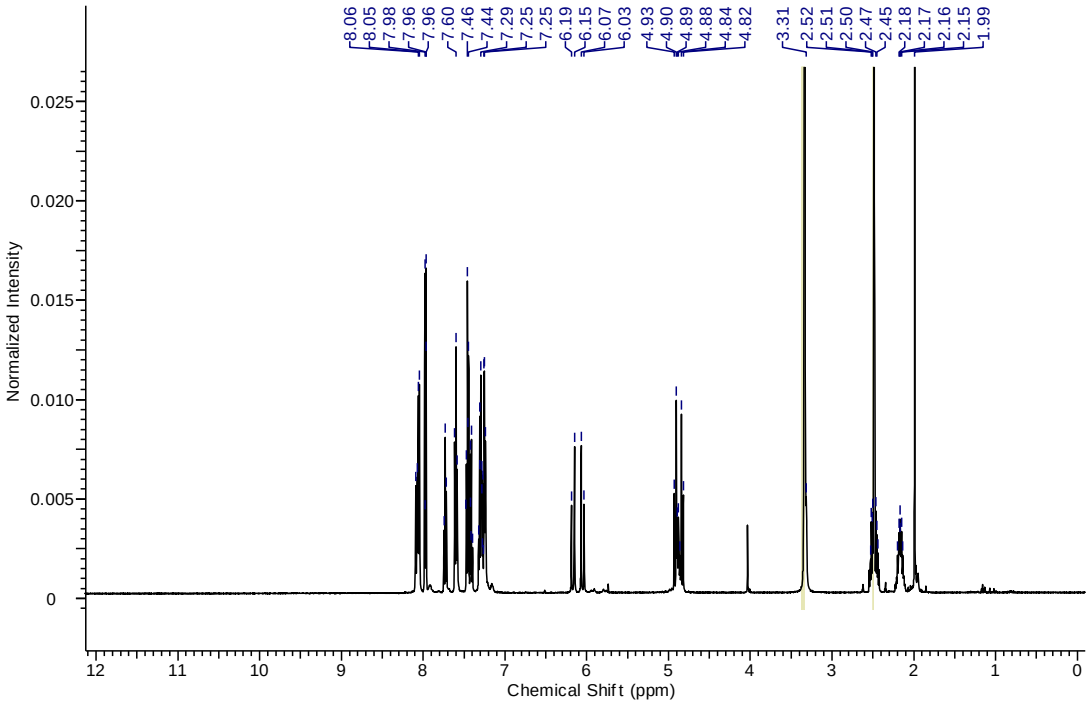


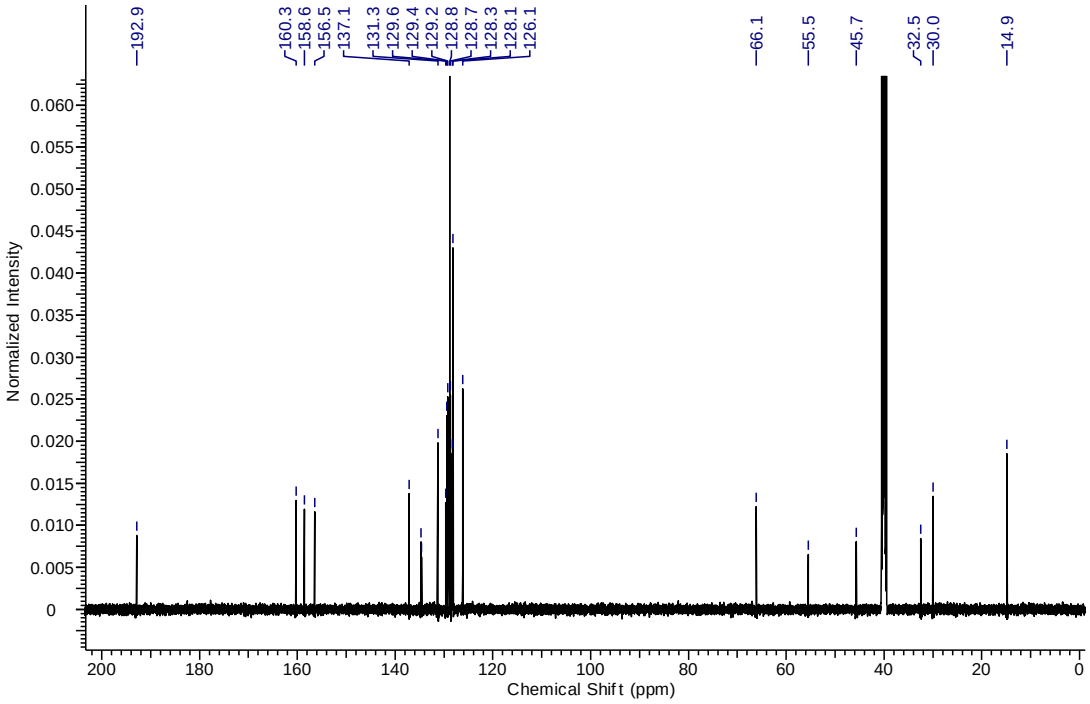
Benzyl (S)-2-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)pyrrolidine-1-carboxylate (129)



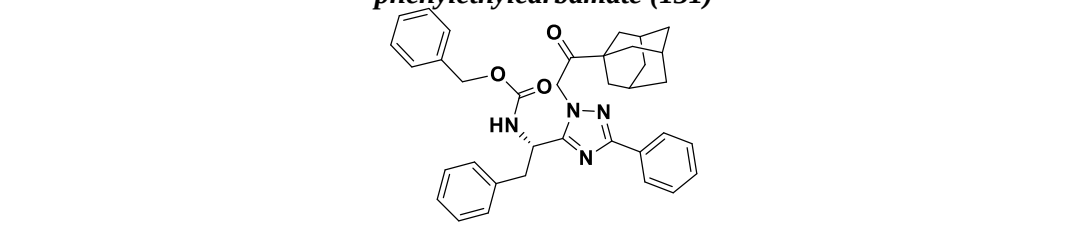
Benzyl (S)-(3-(methylthio)-1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)propyl)carbamate (130)

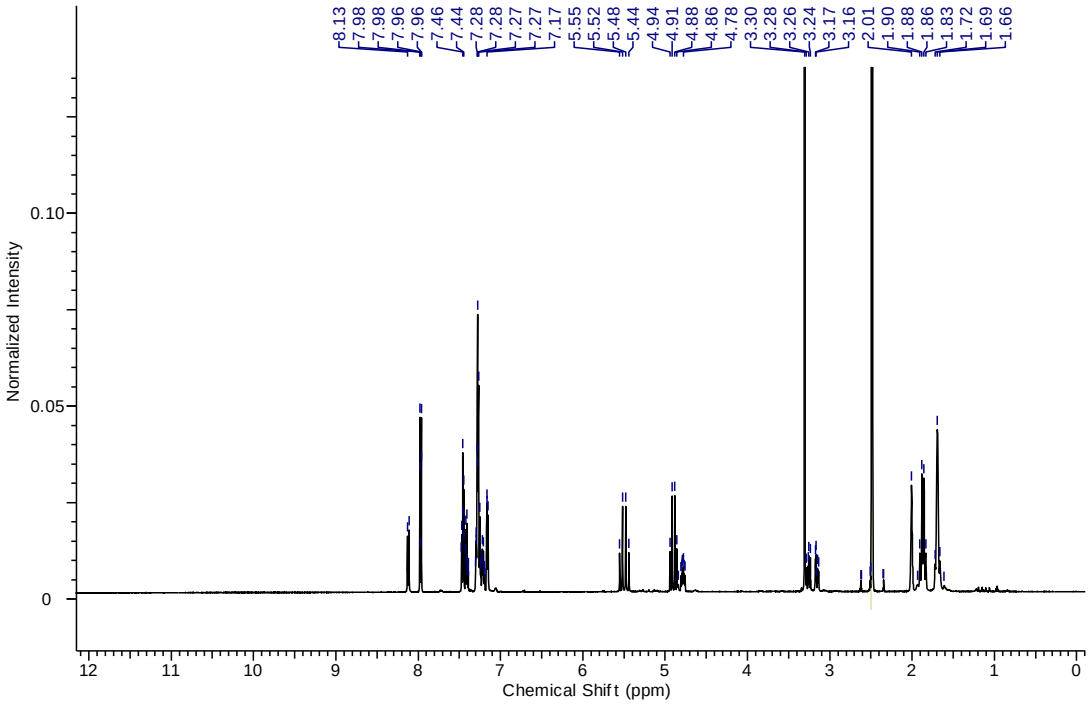


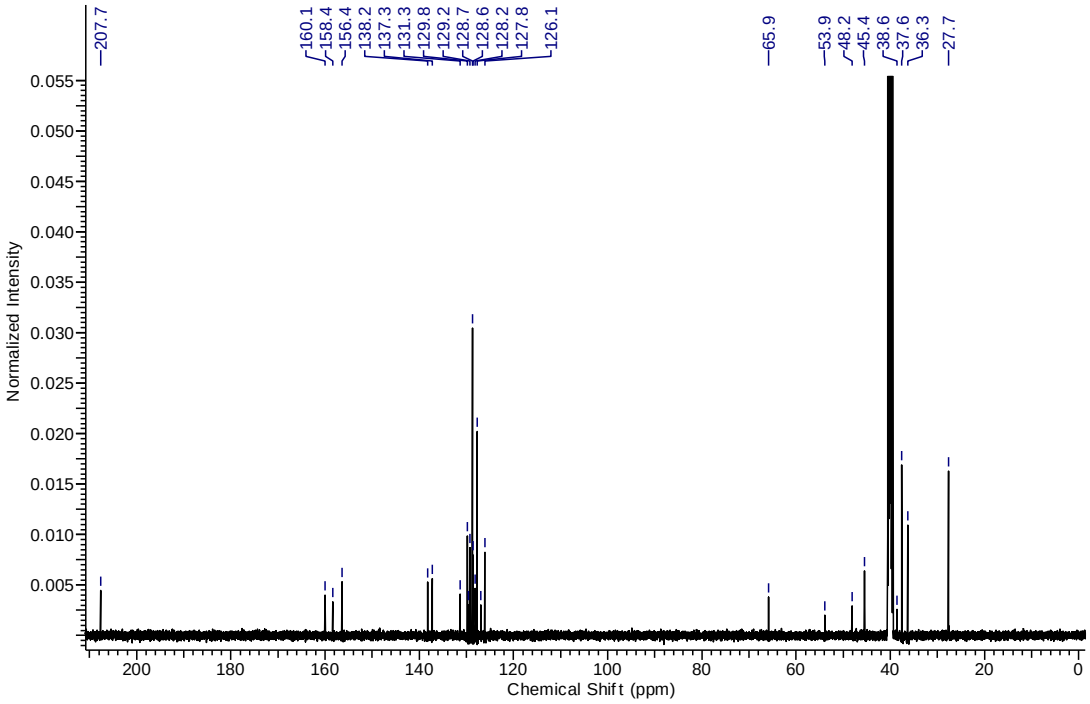




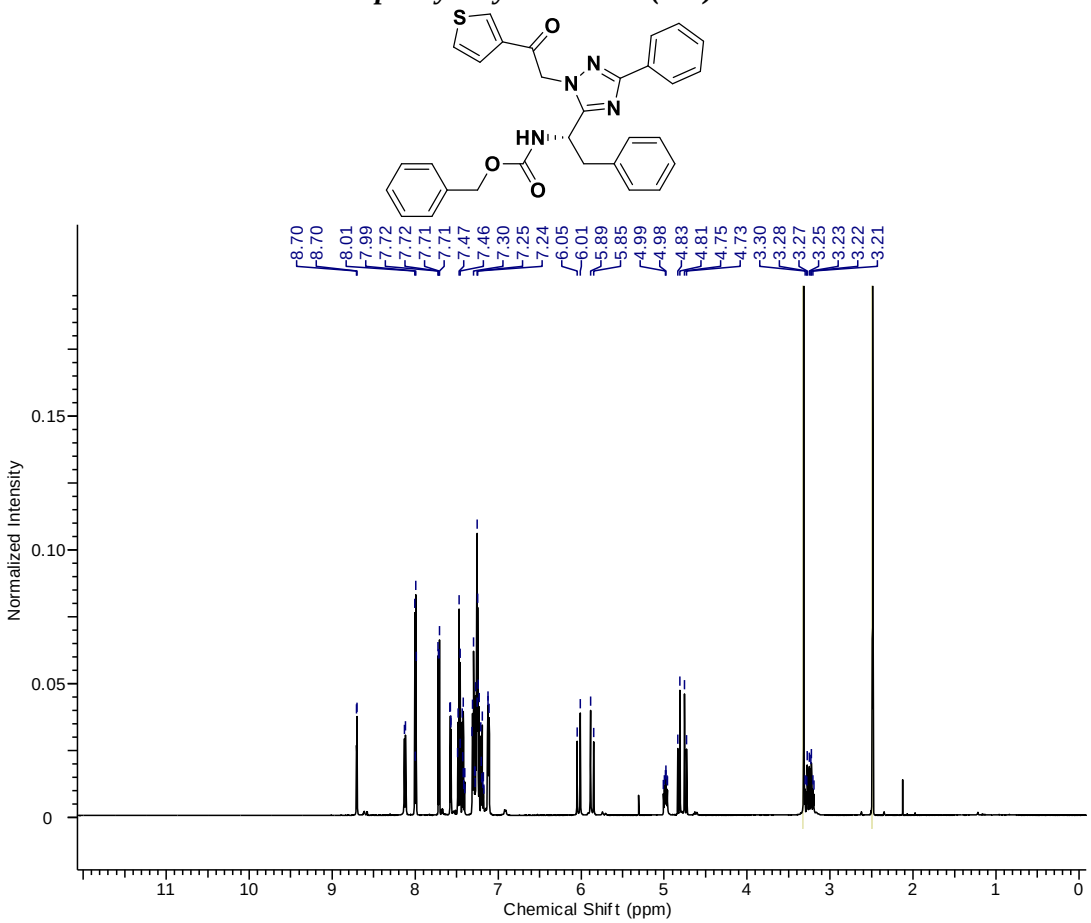
(S)-benzyl-1-(1-(2-oxo-2-((1R,3R)-adamant-1-yl)ethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethylcarbamate (131)

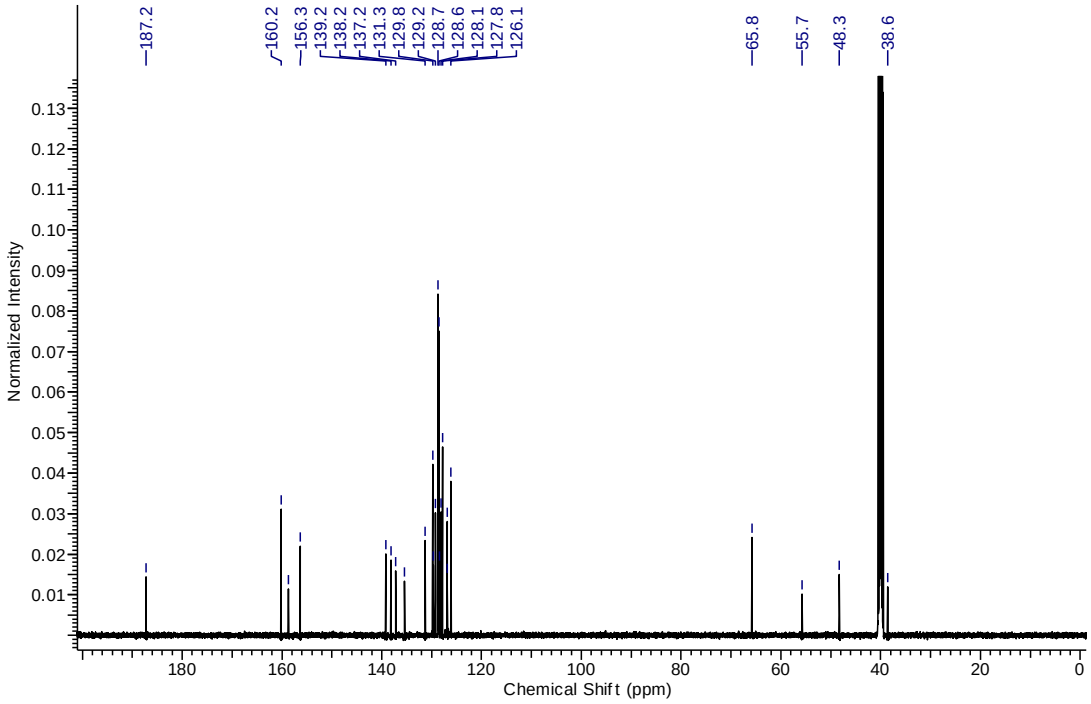




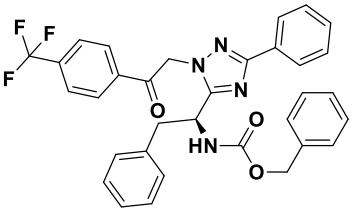


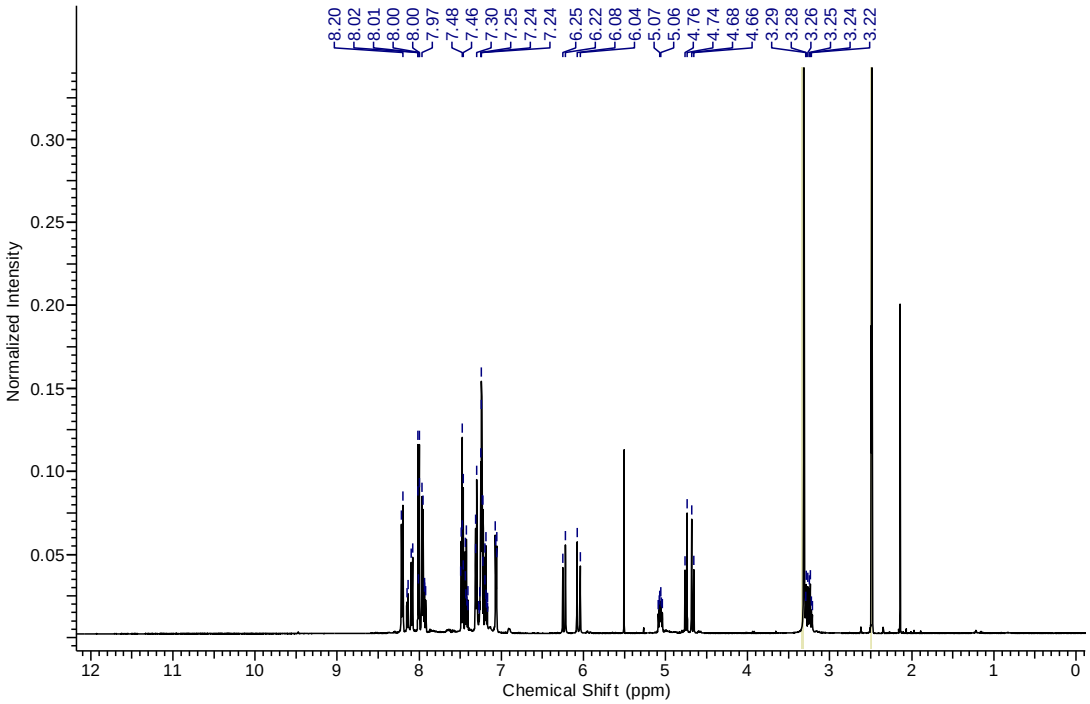
(S)-benzyl 1-(1-(2-oxo-2-(thiophen-3-yl)ethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethylcarbamate (132)

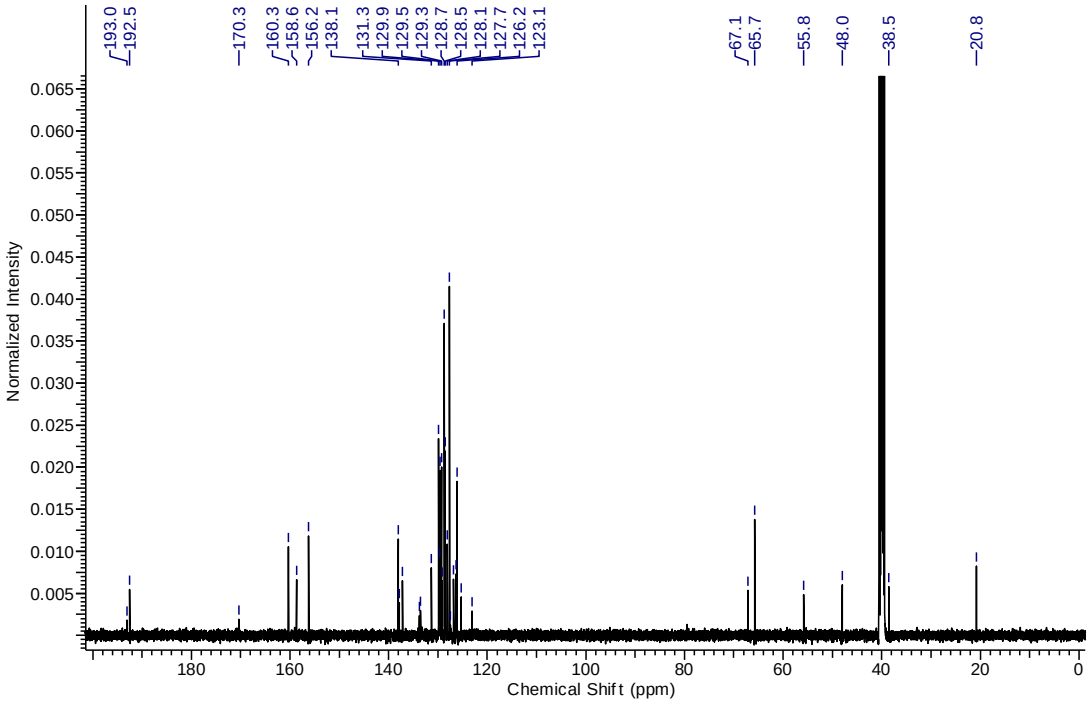




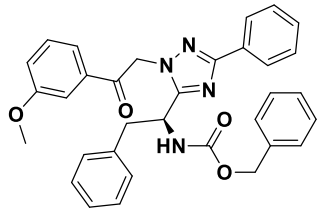
(S)-benzyl 1-(1-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethylcarbamate (133)

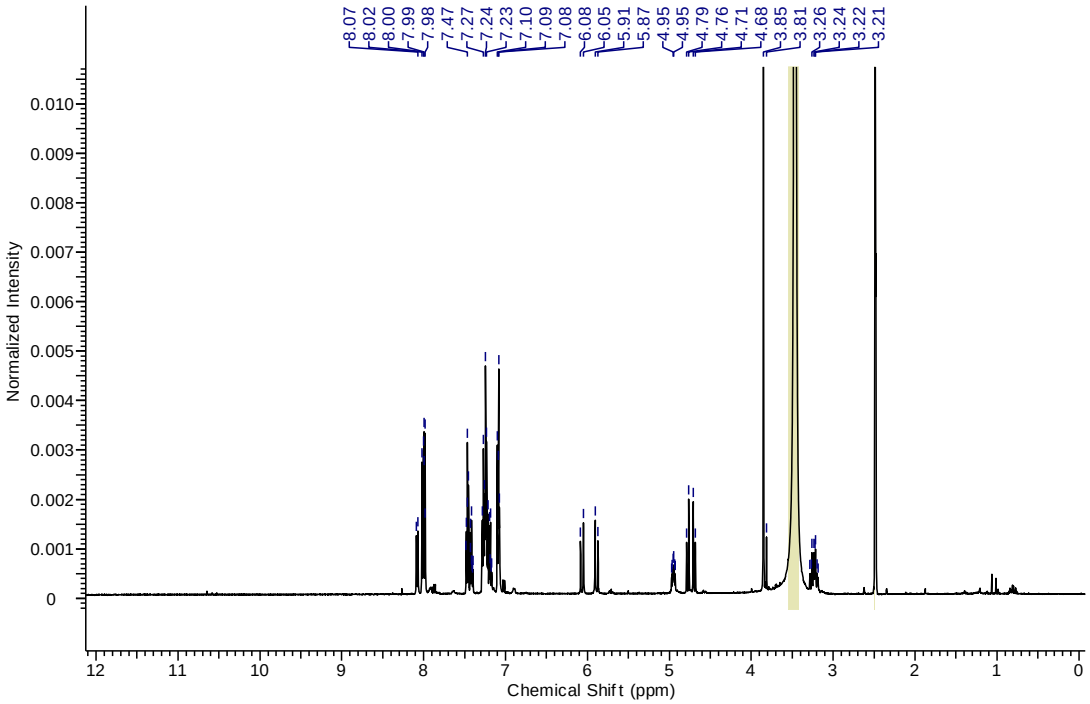


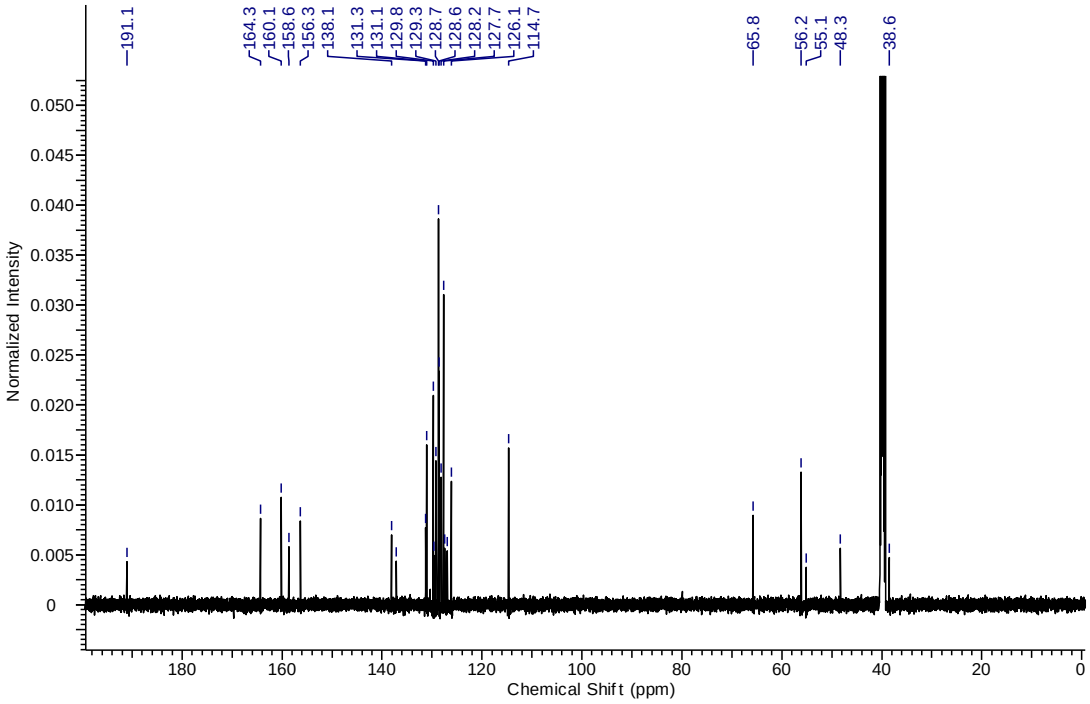




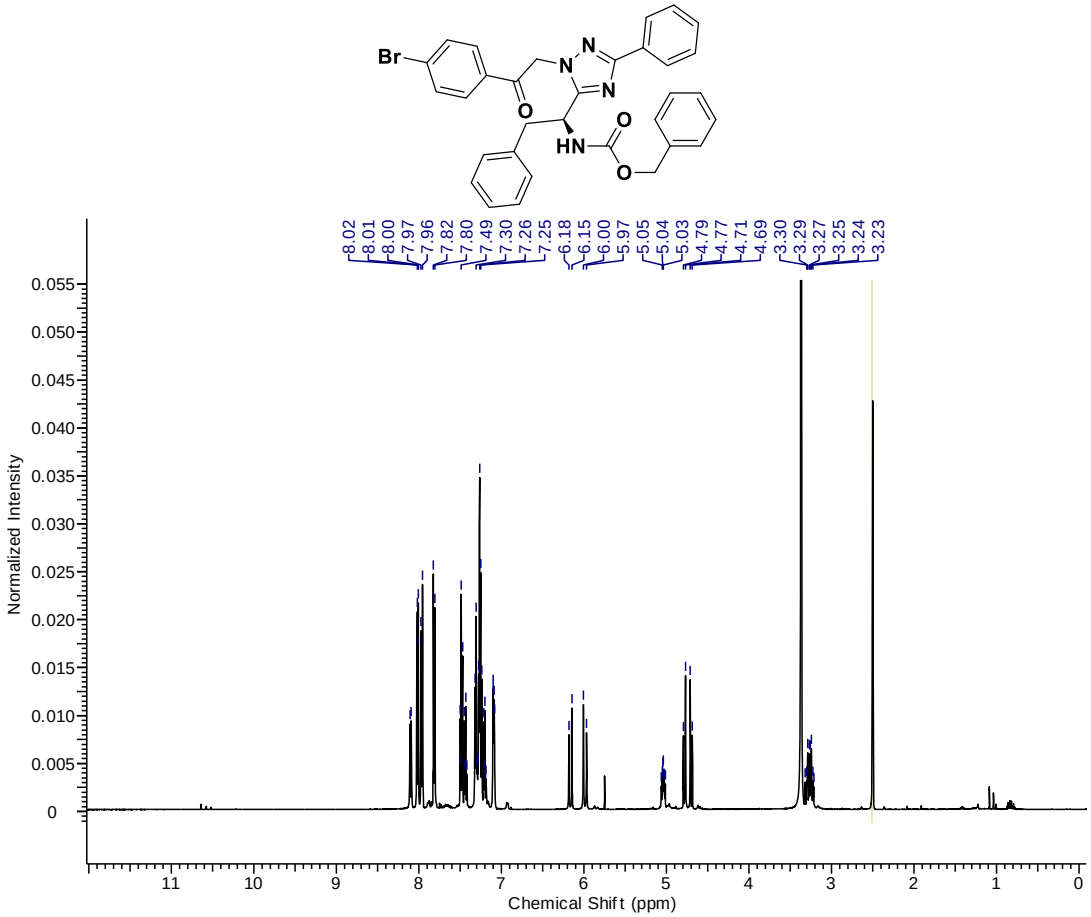
Benzyl (S)-(1-(1-(2-(4-methoxyphenyl)-2-oxoethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (134)

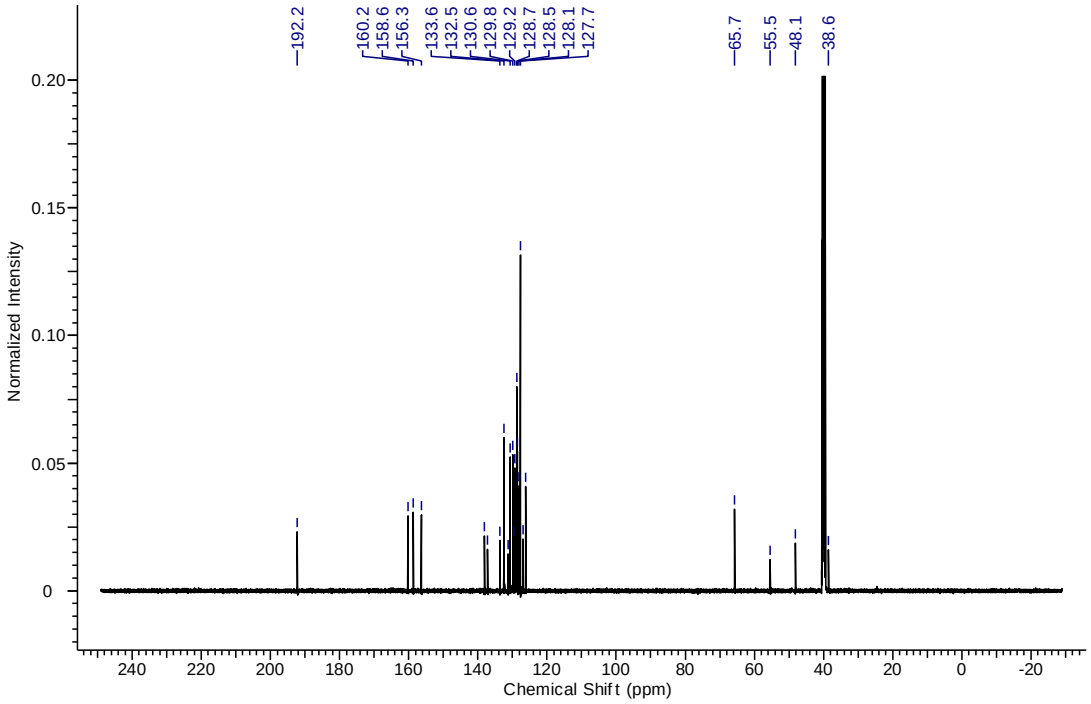




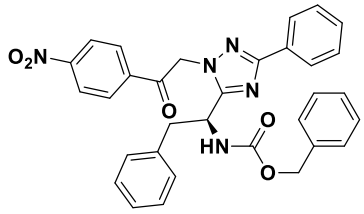


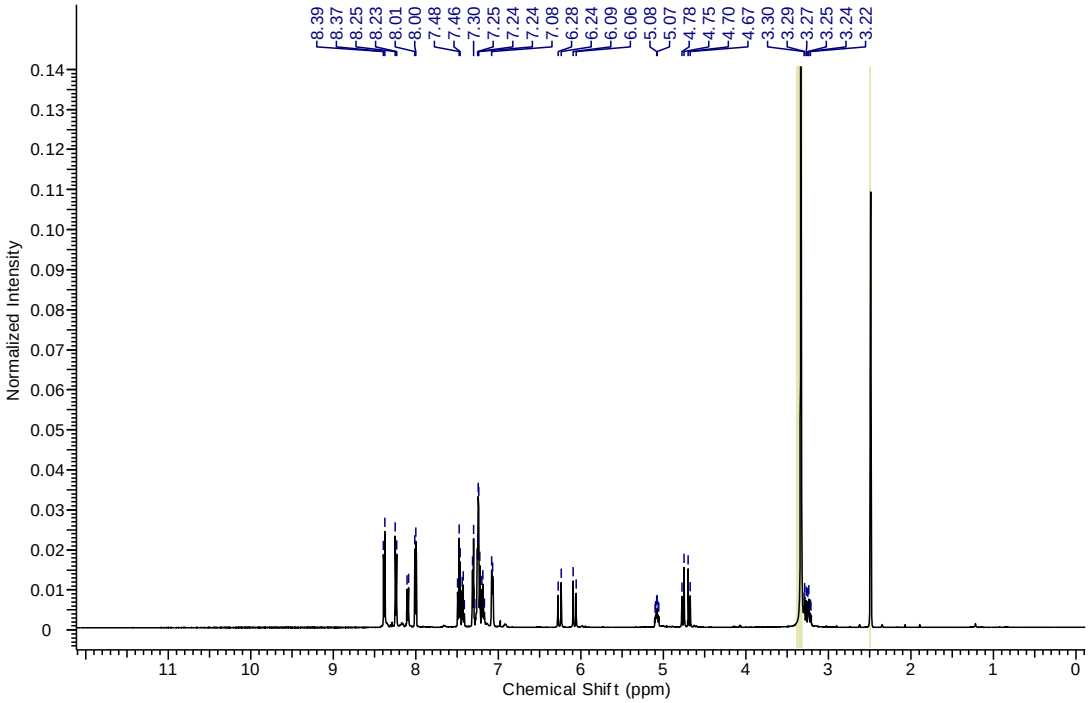
Benzyl (S)-(1-(1-(2-(4-bromophenyl)-2-oxoethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (135)

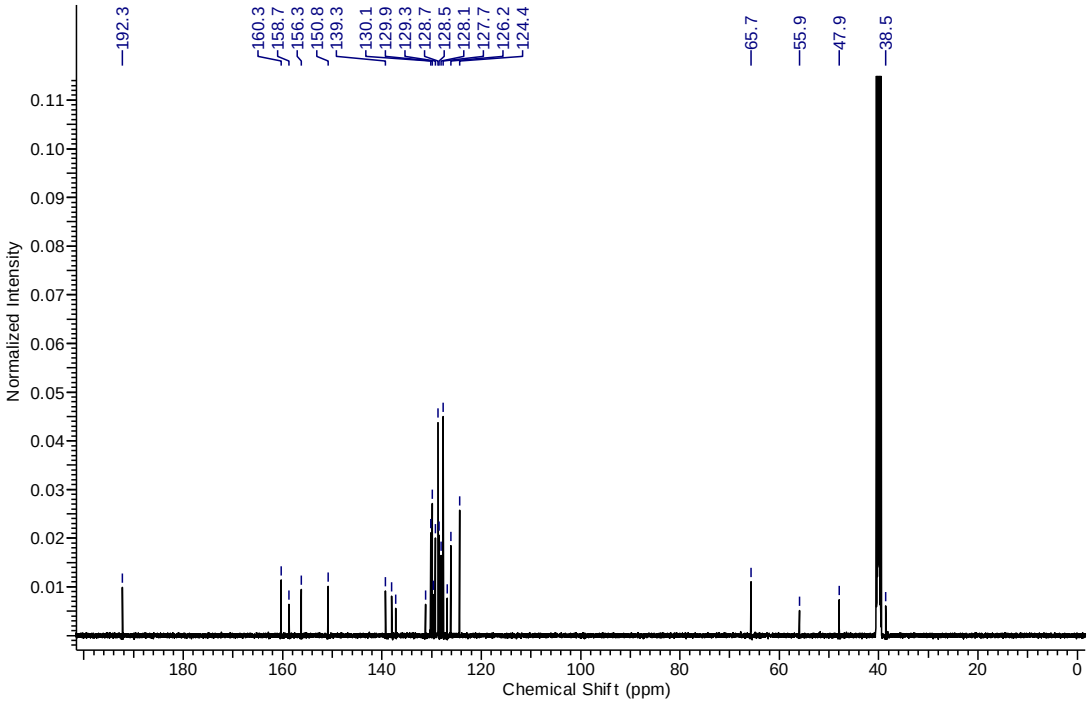




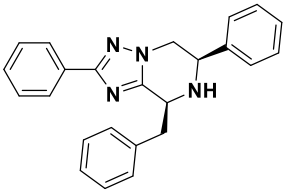
Benzyl (S)-(1-(1-(2-(4-nitrophenyl)-2-oxoethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (136)

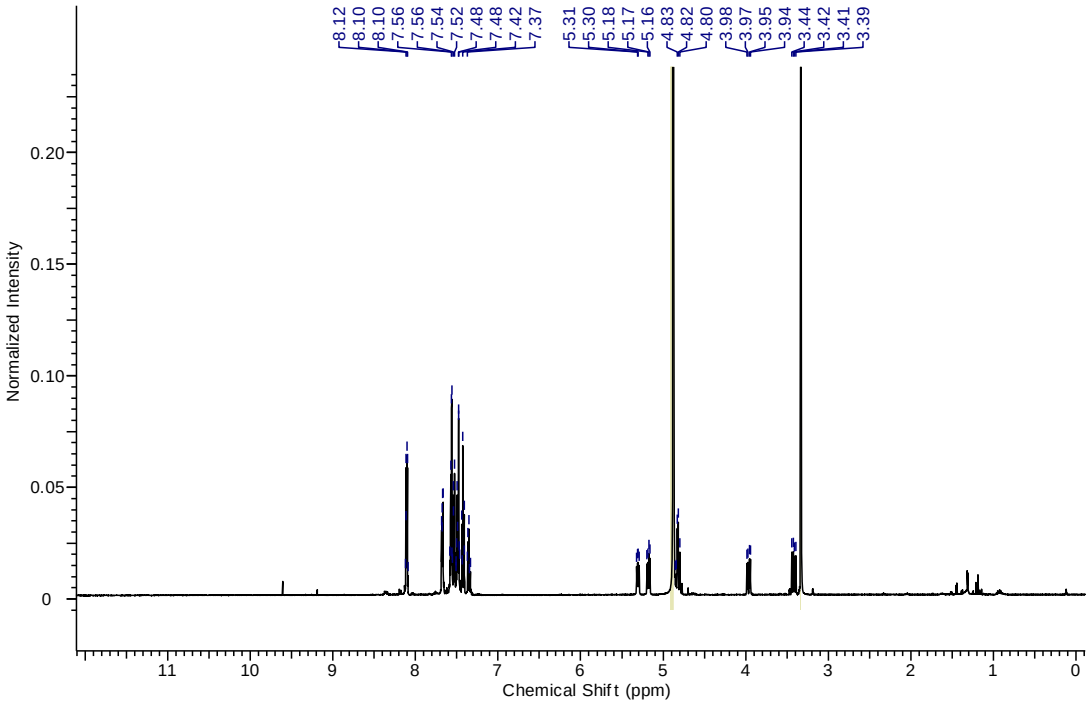


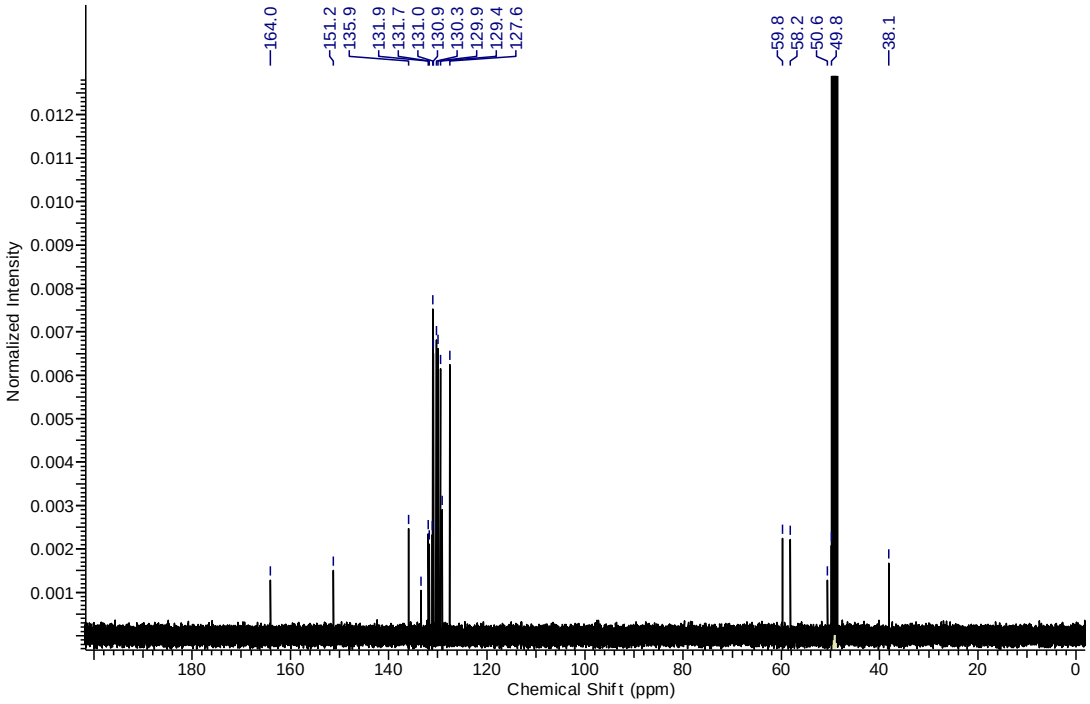




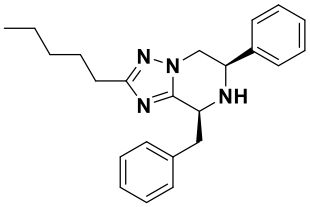
(6R,8S)-8-benzyl-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (58)

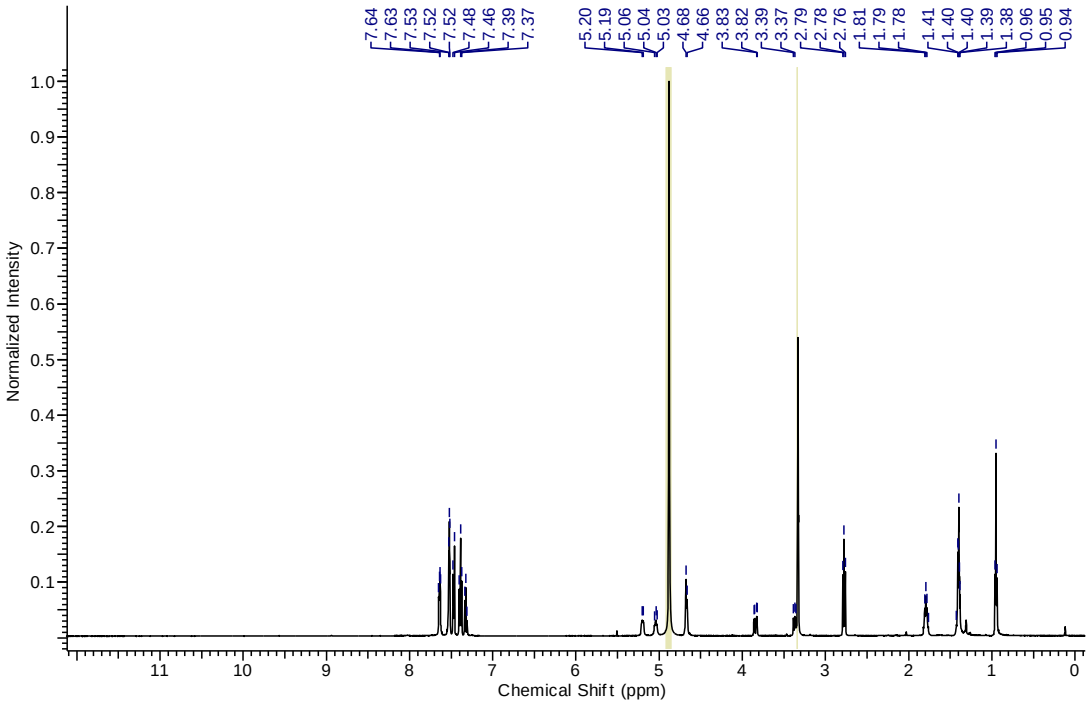


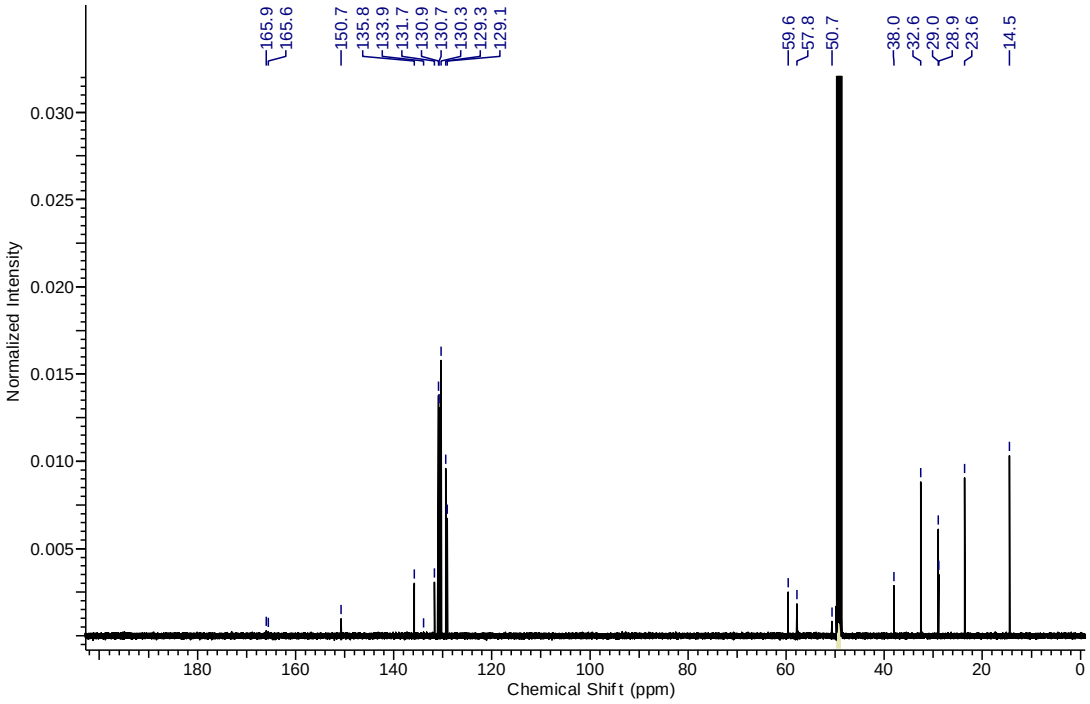




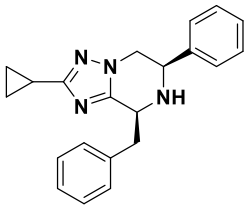
(6R,8S)-8-benzyl-2-pentyl-6-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (137)

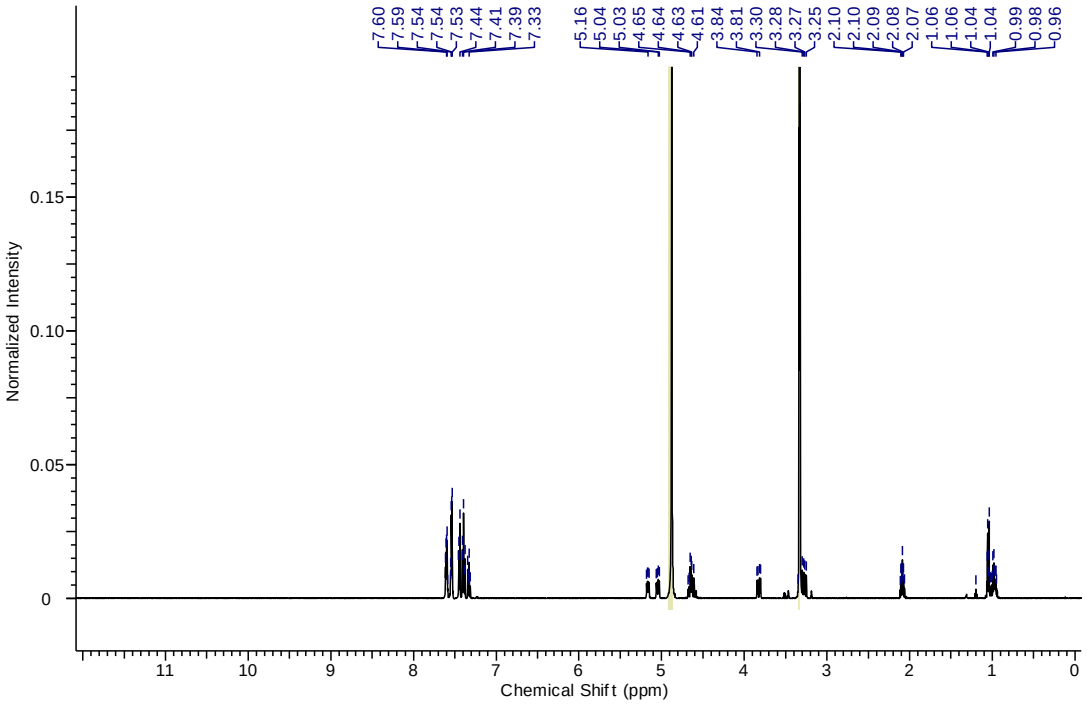


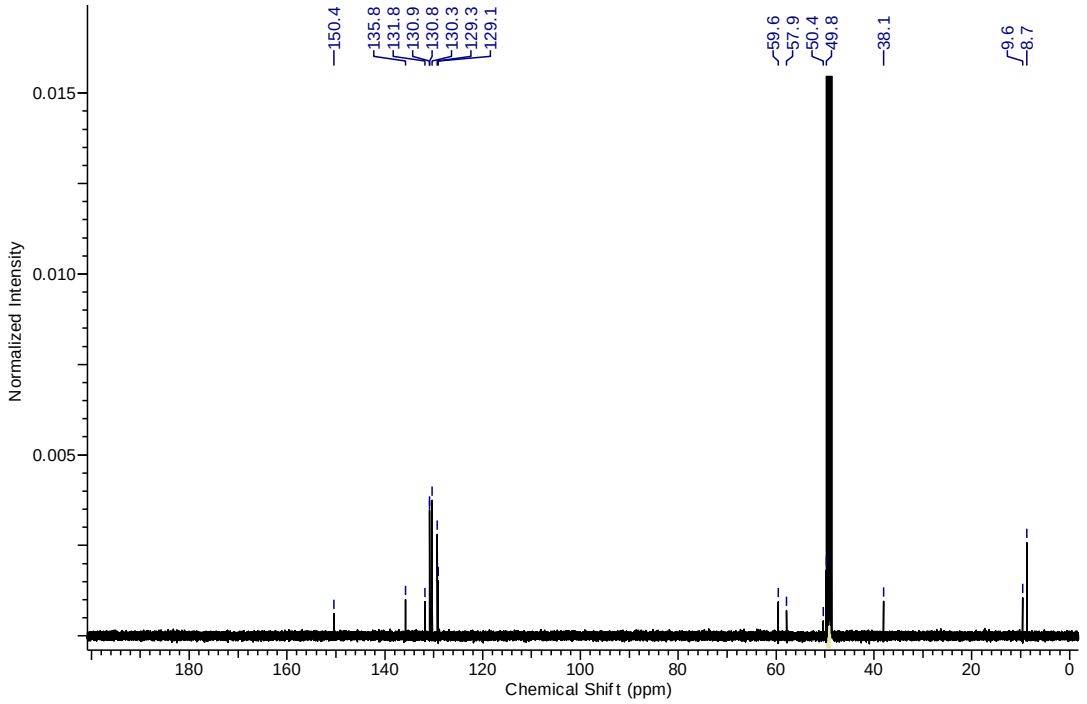




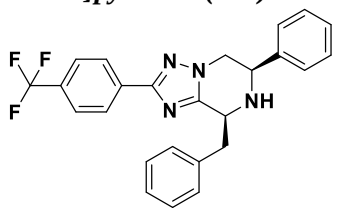
(6R,8S)-8-benzyl-6-cyclopropyl-6-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (138)

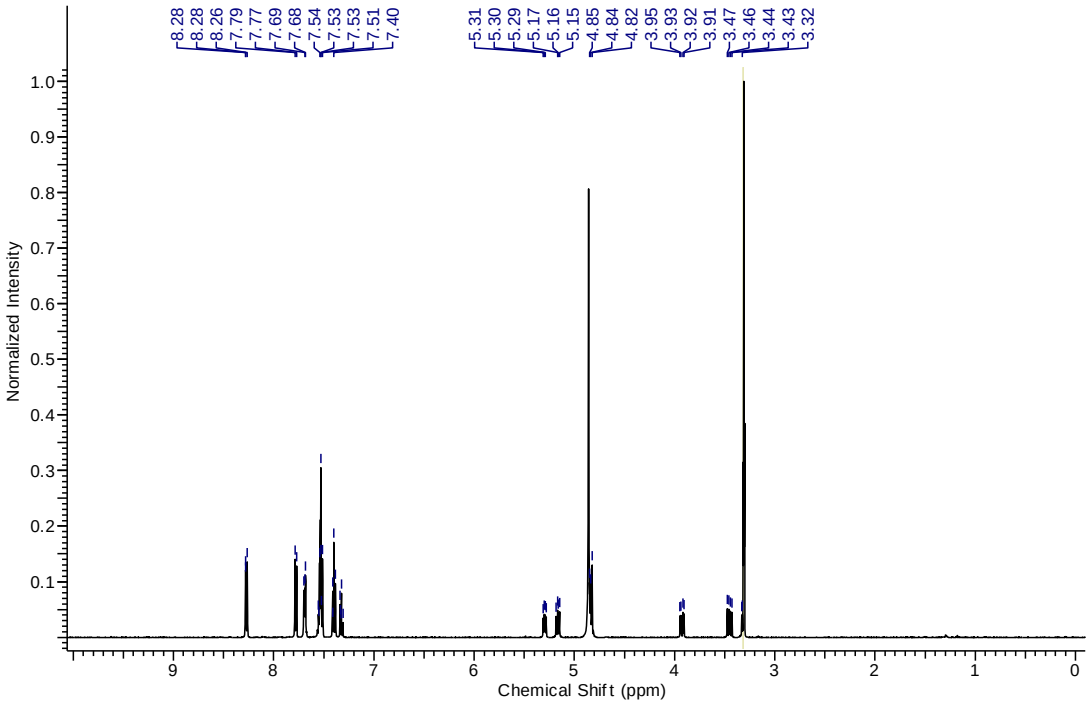


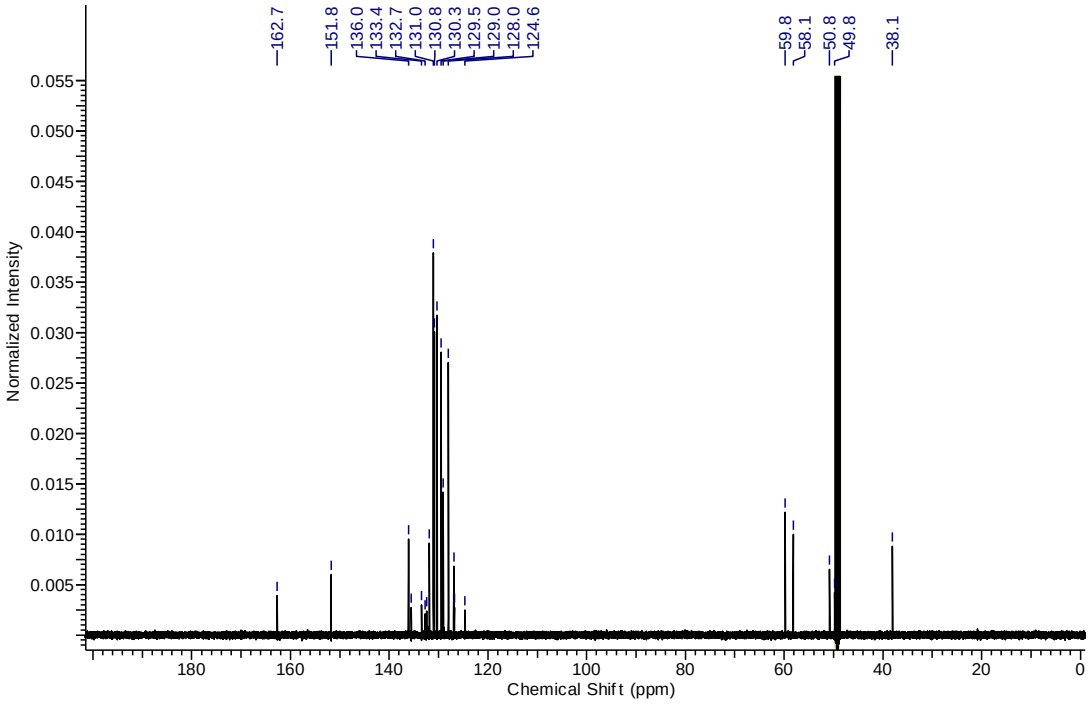




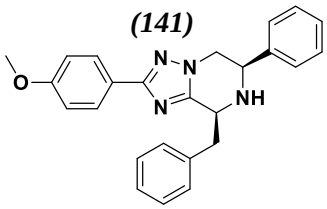
(6R,8S)-8-benzyl-6-phenyl-2-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (139)

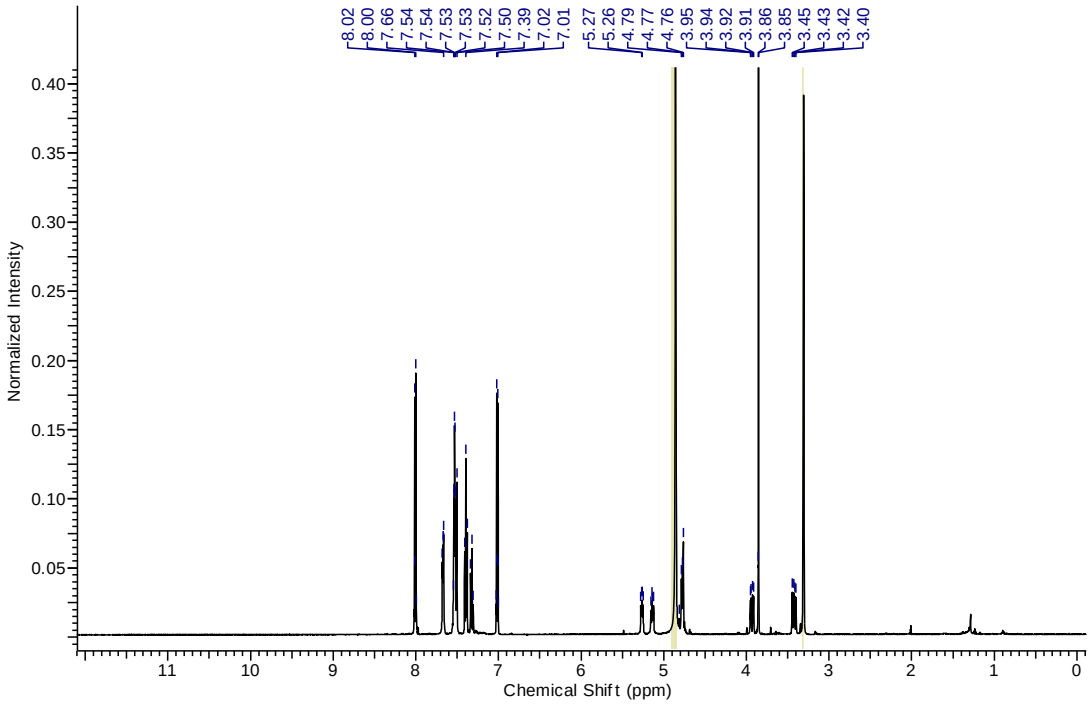


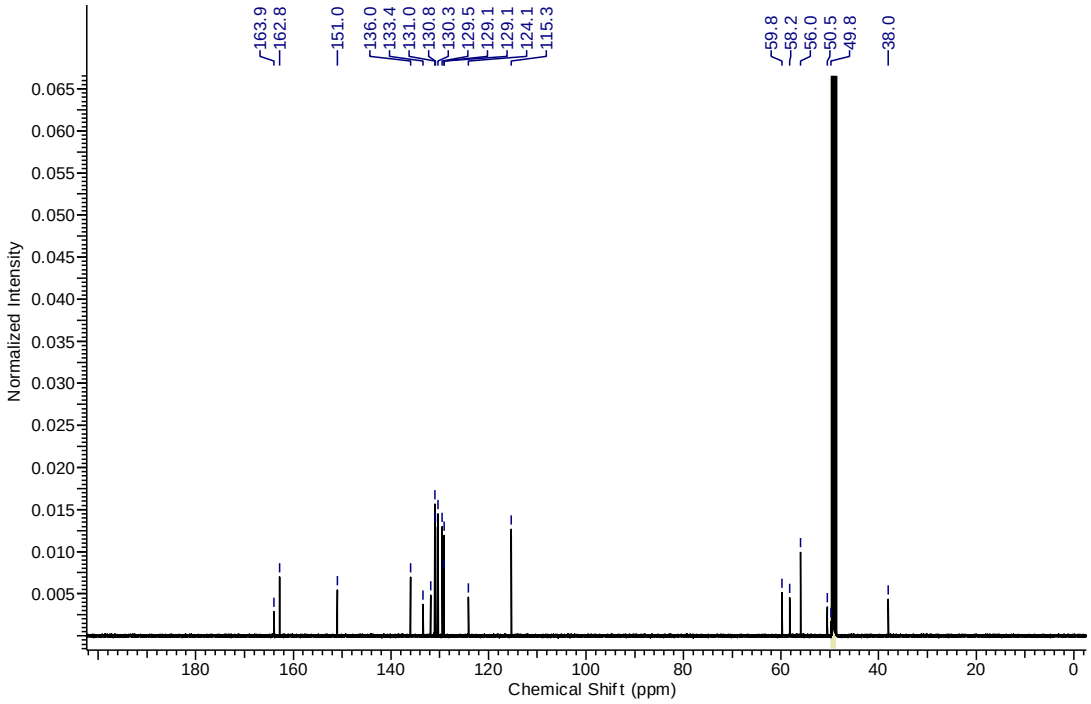




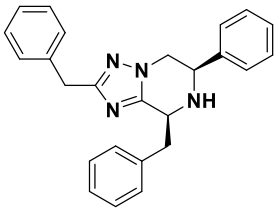
(6R,8S)-8-benzyl-2-(4-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (141)

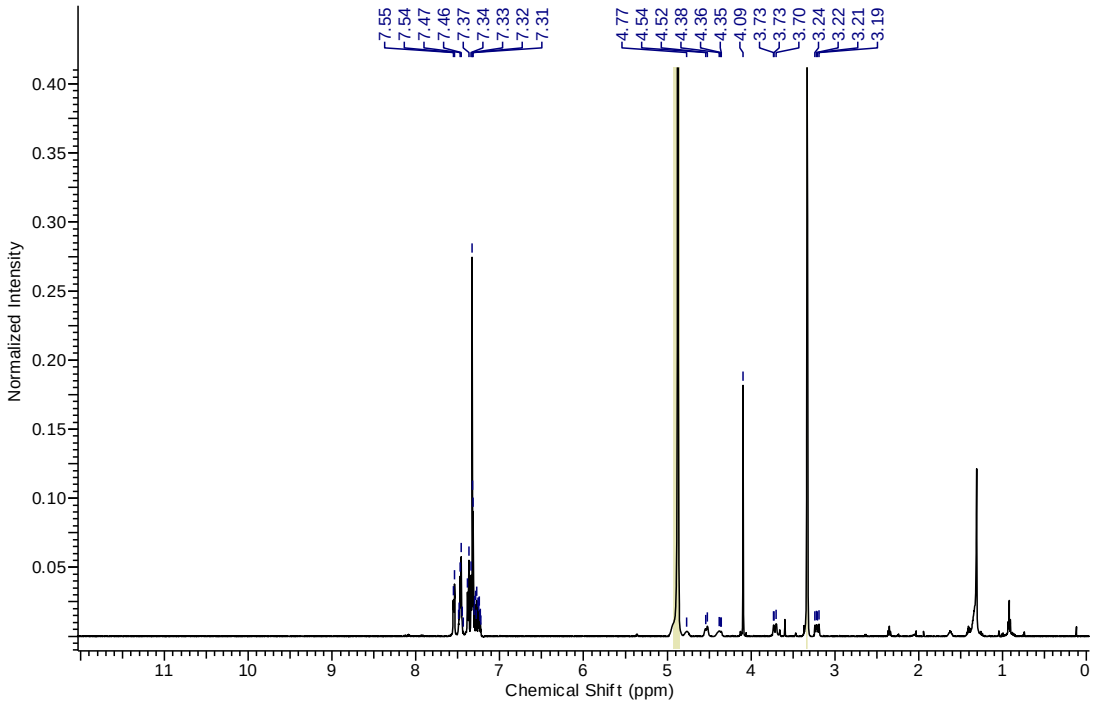


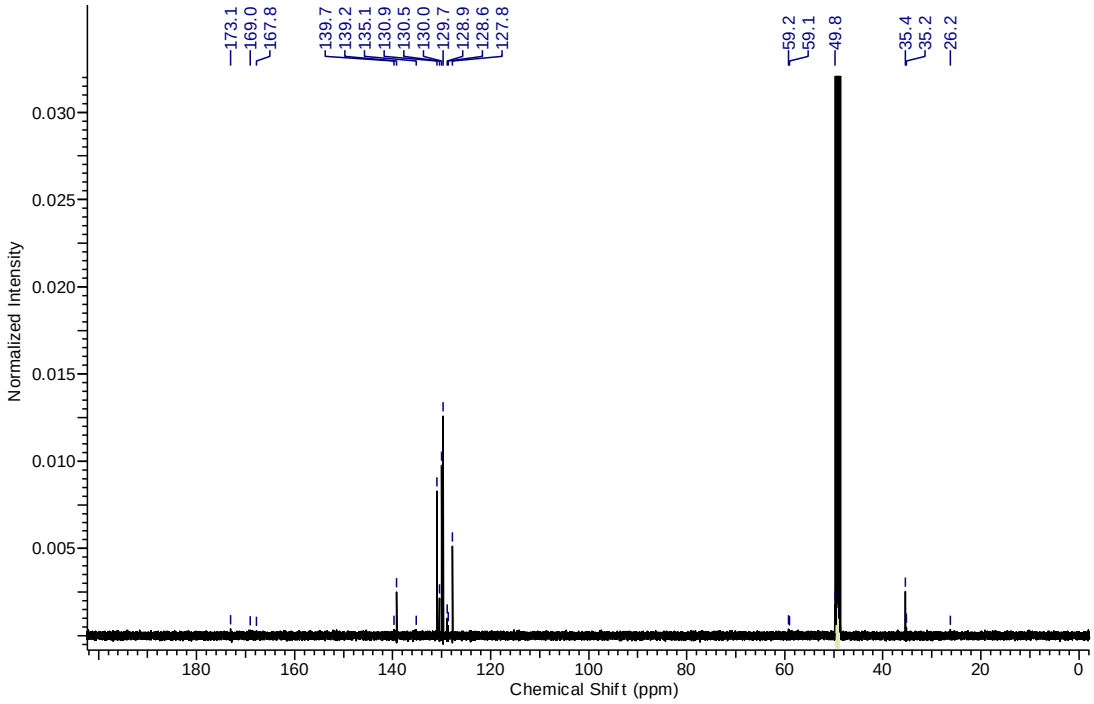




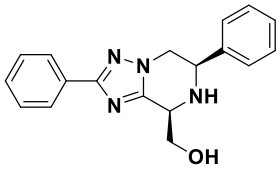
(6R,8S)-2,8-dibenzyl-6-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (142)

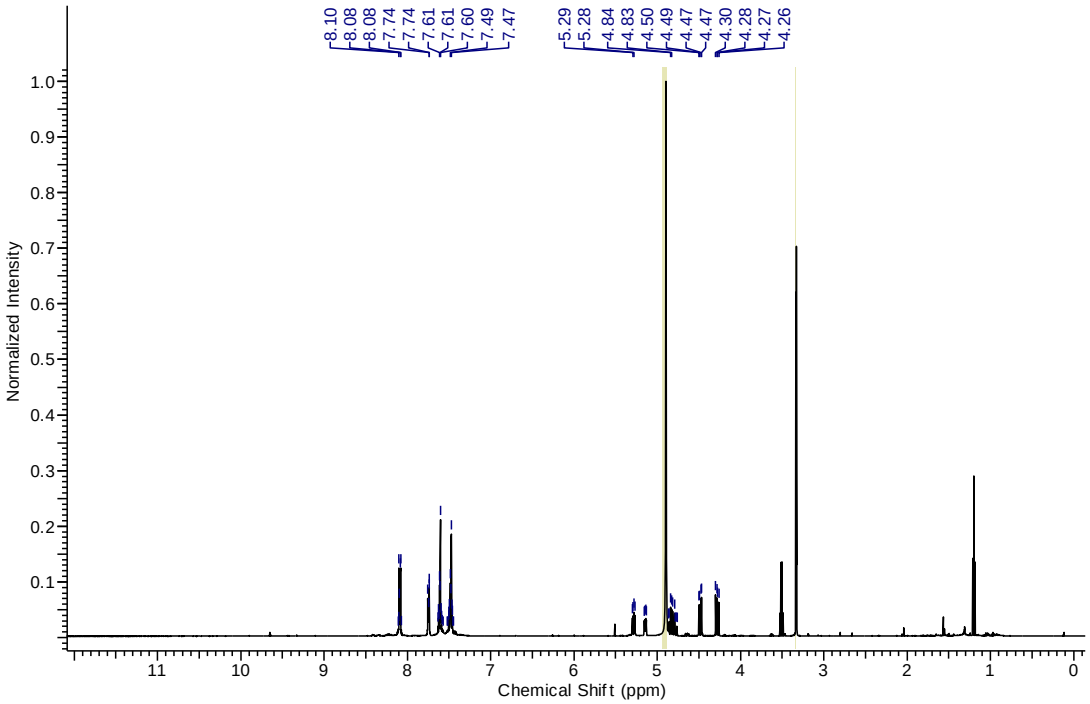


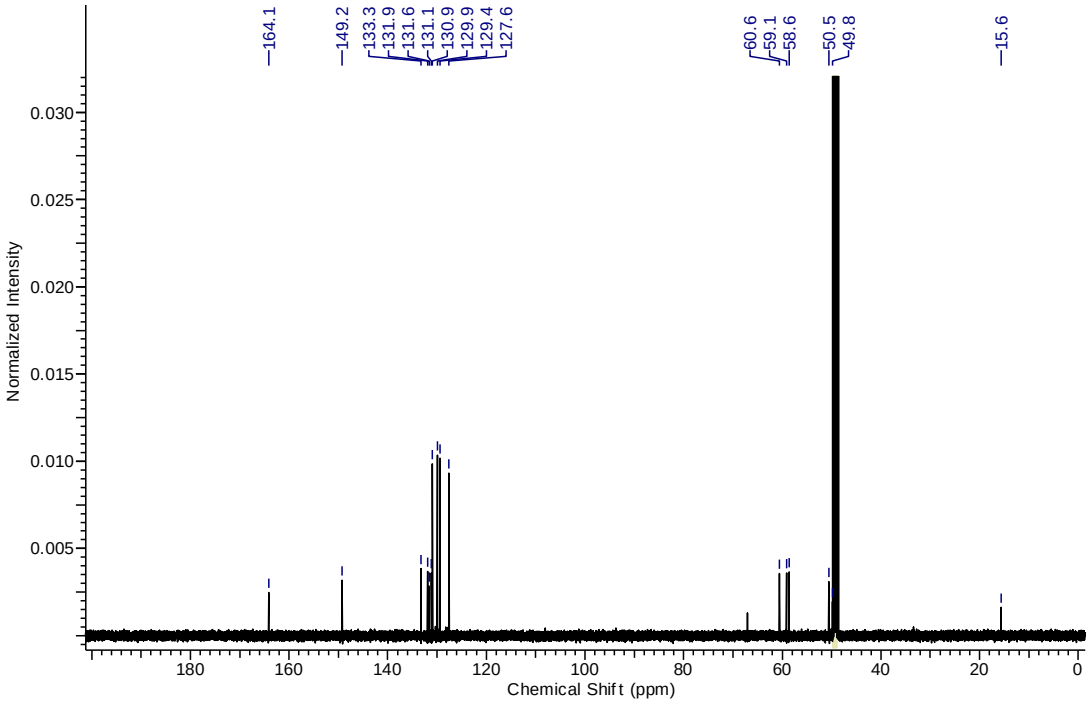




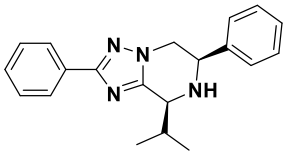
((6R,8R)-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazin-8-yl)methanol (143)

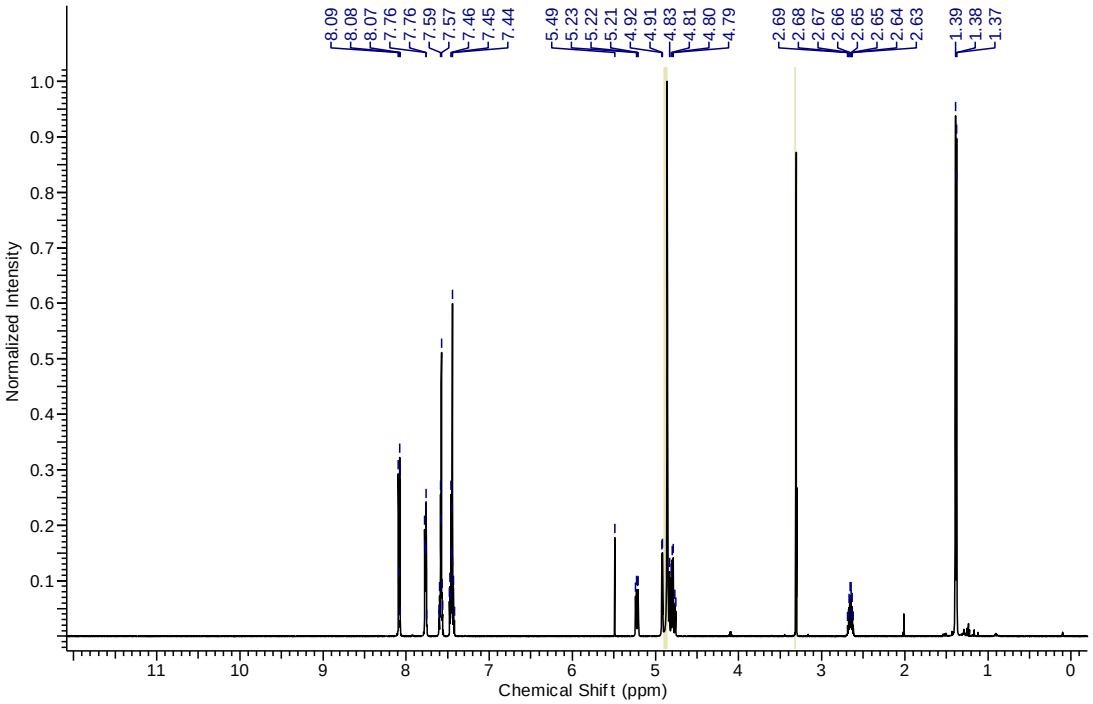


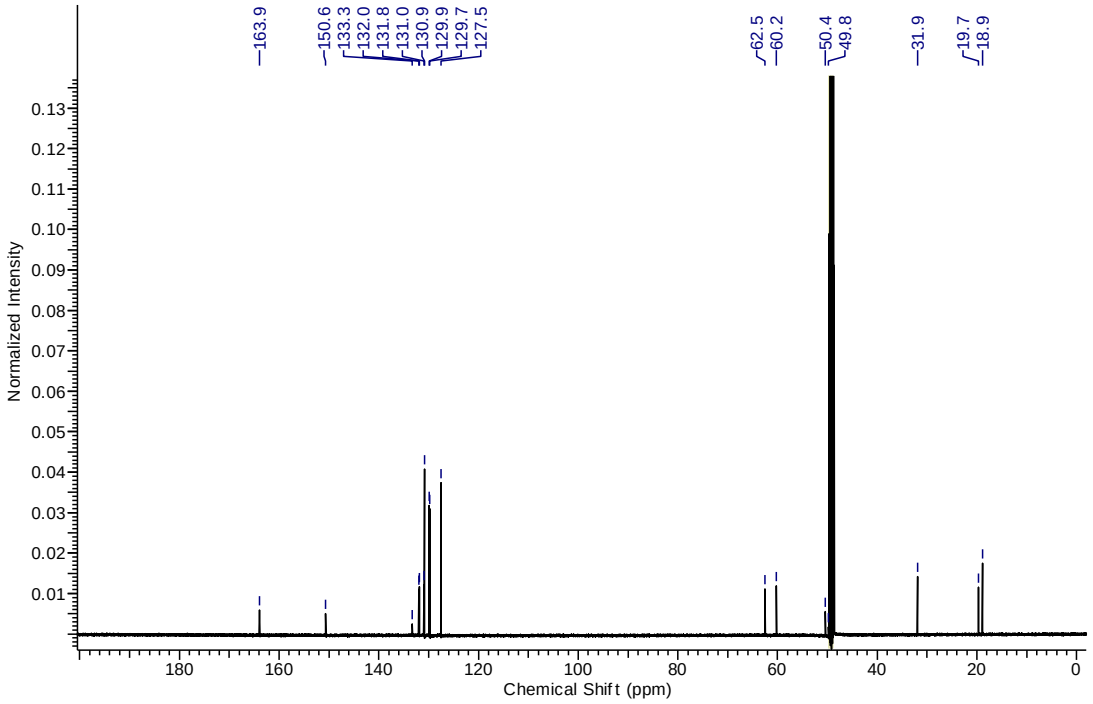




(6R,8S)-8-isopropyl-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (144)

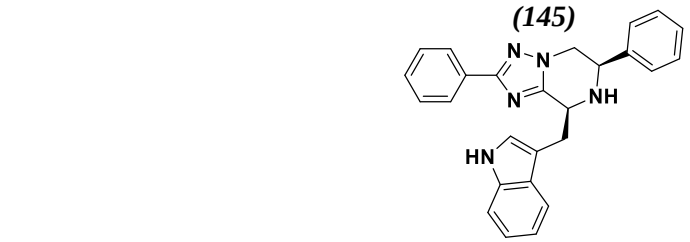


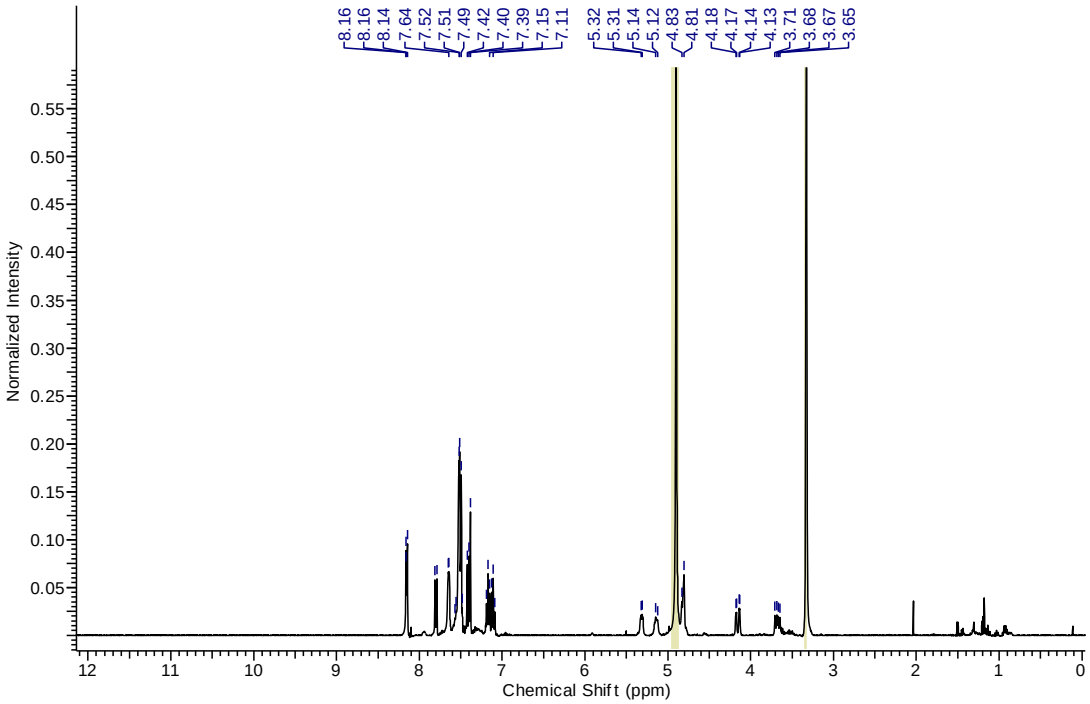


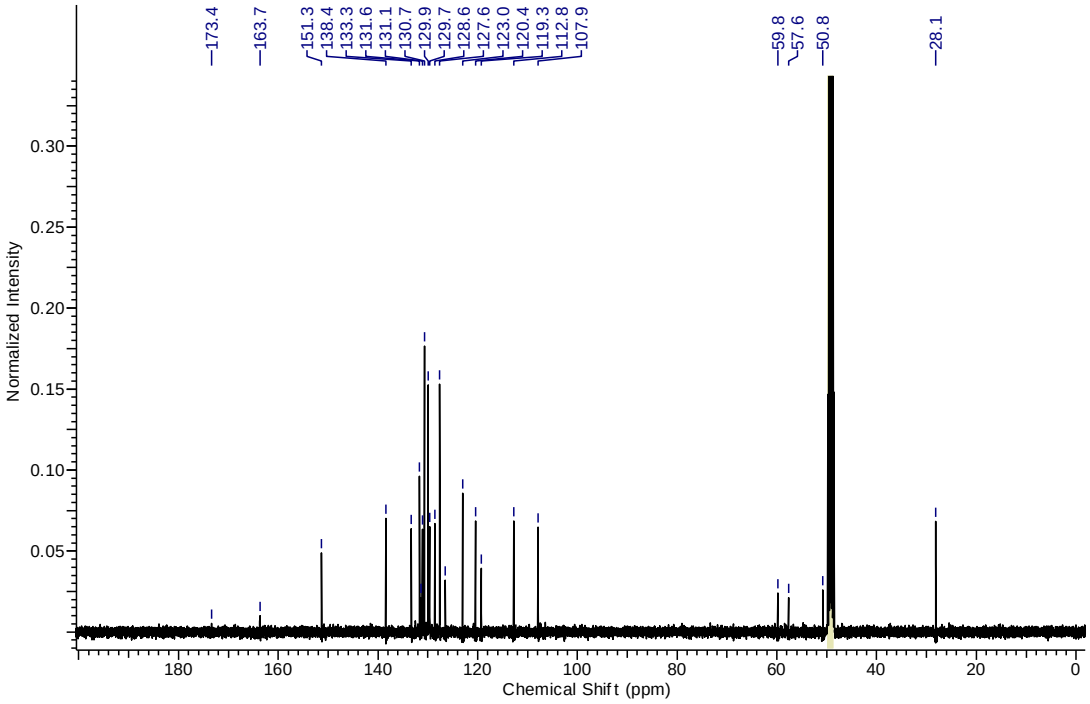


(6R,8S)-8-((1H-indol-3-yl)methyl)-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine

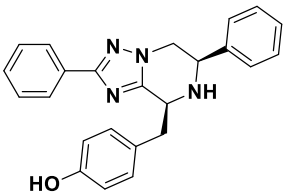
(145)

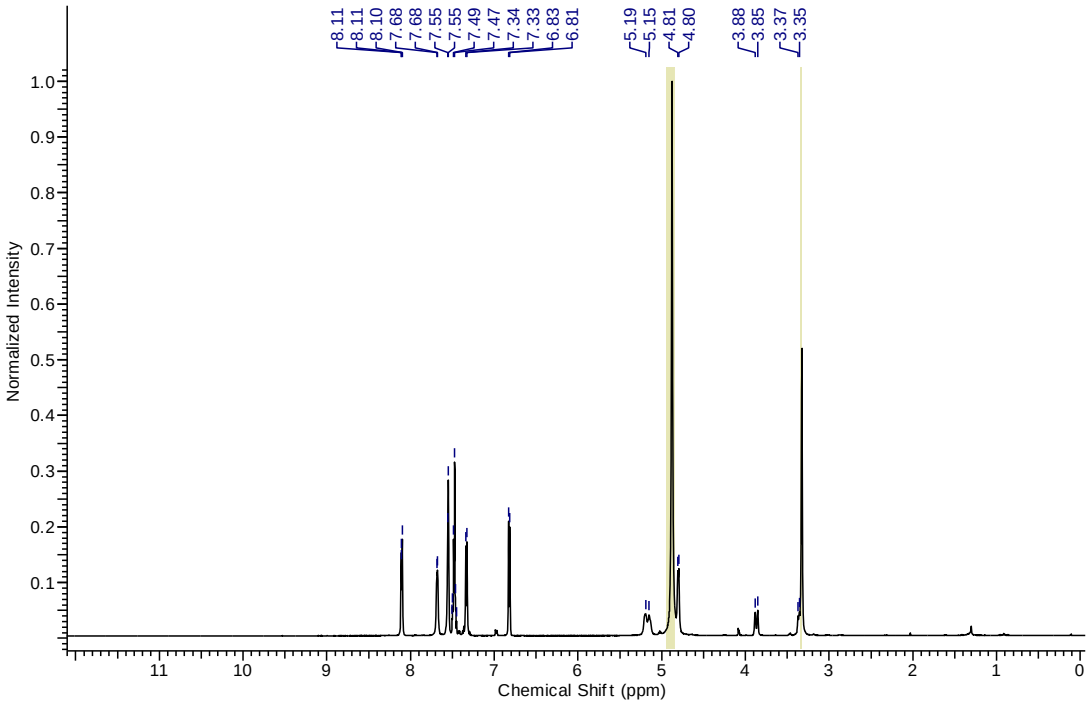


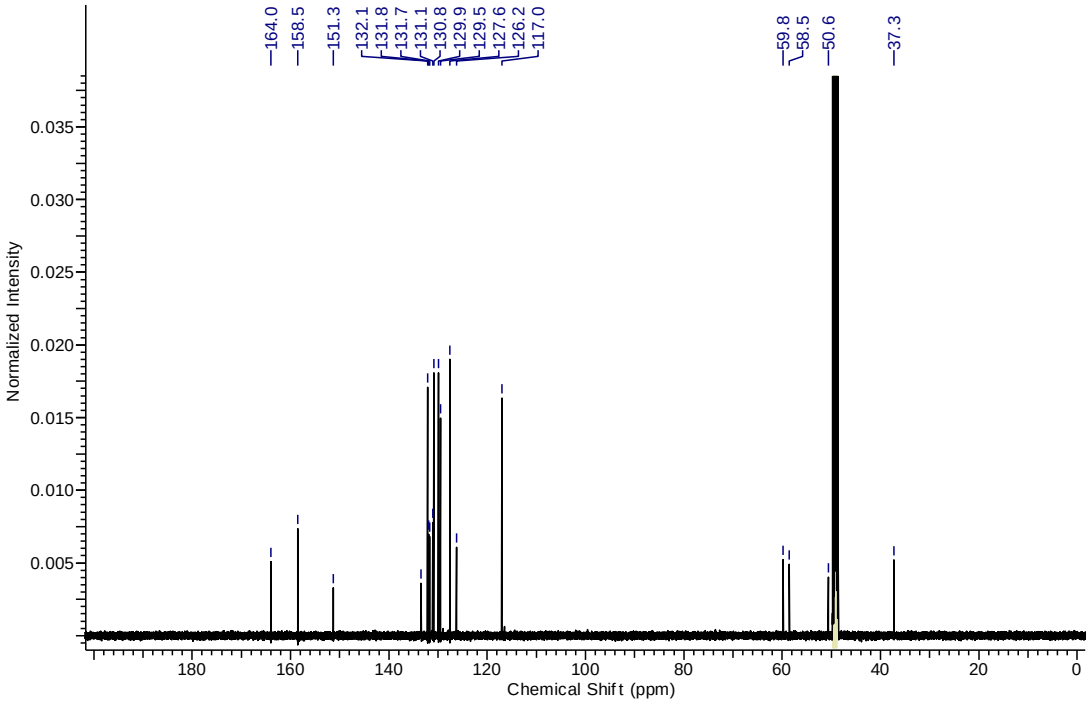




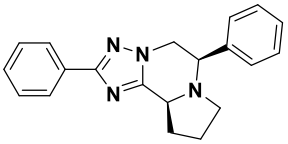
4-(((6R,8S)-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazin-8-yl)methyl)phenol (146)

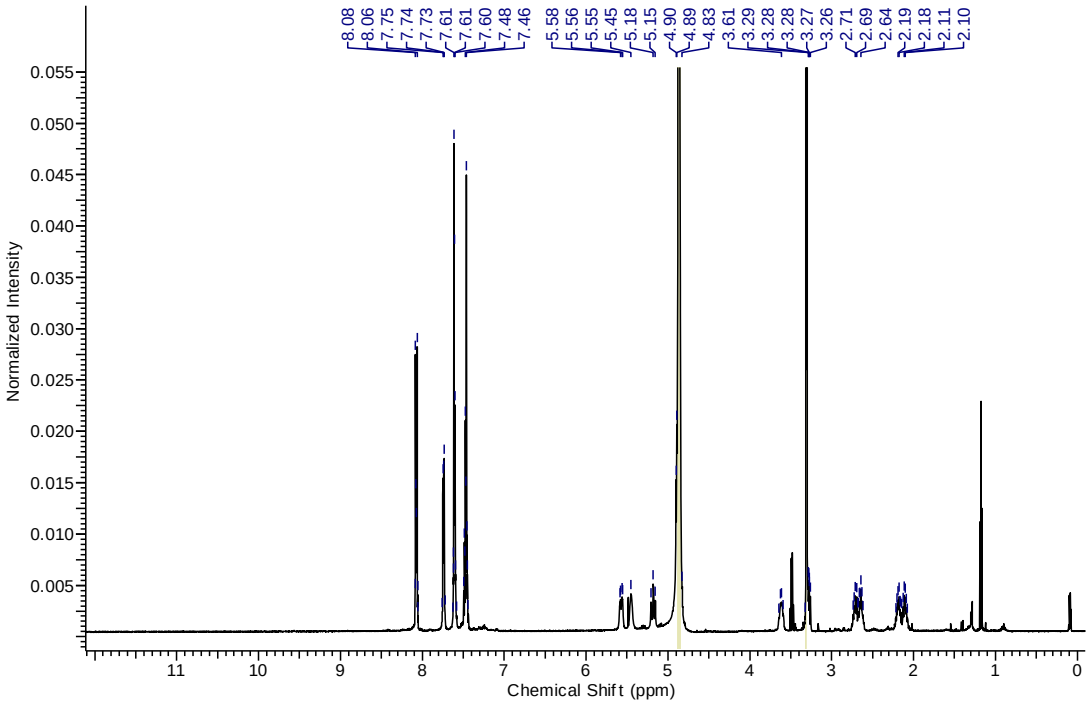


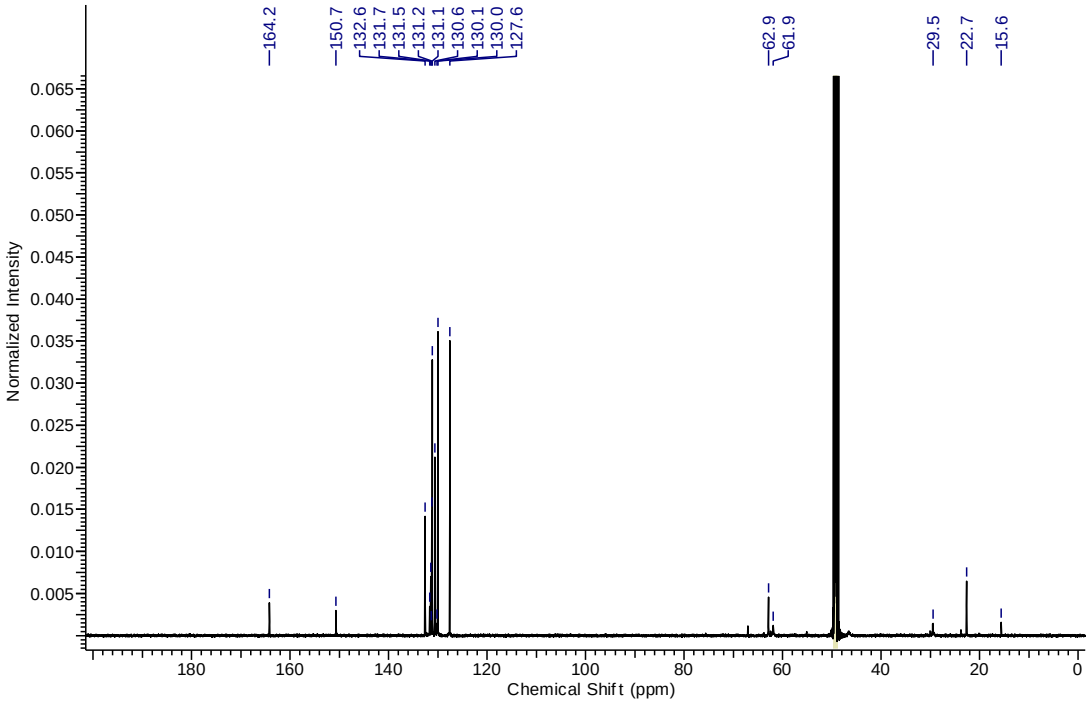




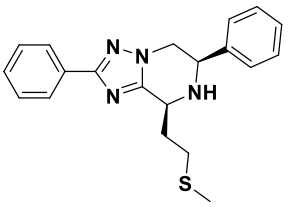
(6R,10aS)-2,6-diphenyl-5,6,8,9,10,10a-hexahydropyrrolo[1,2-a][1,2,4]triazolo[5,1-c]pyrazine (147)

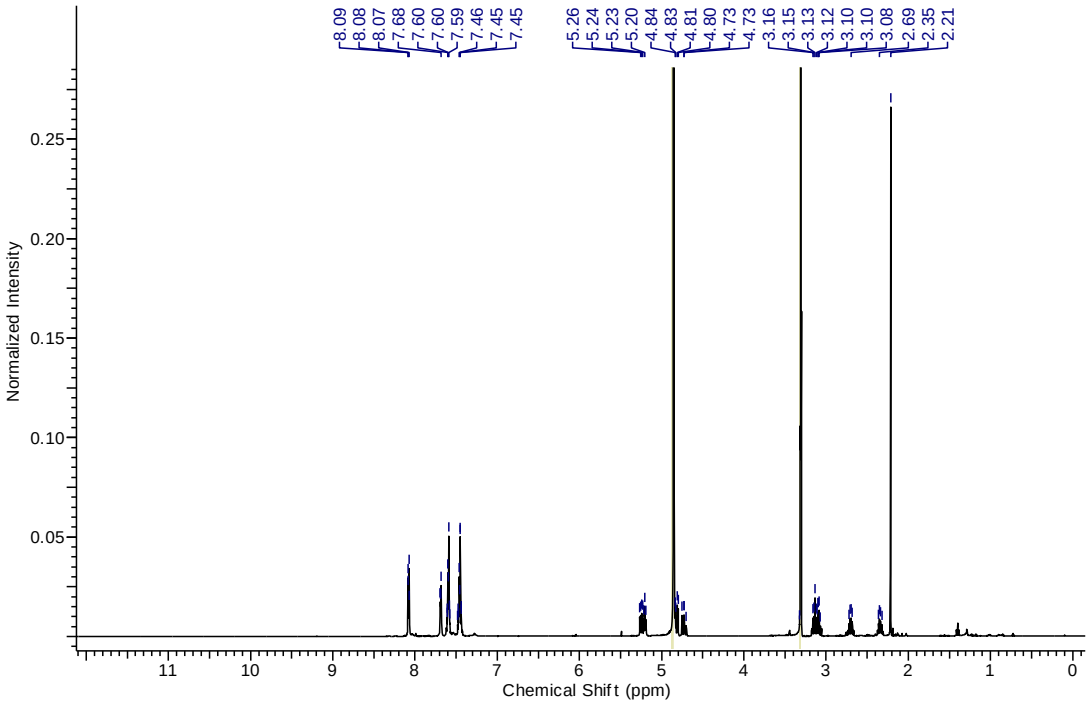


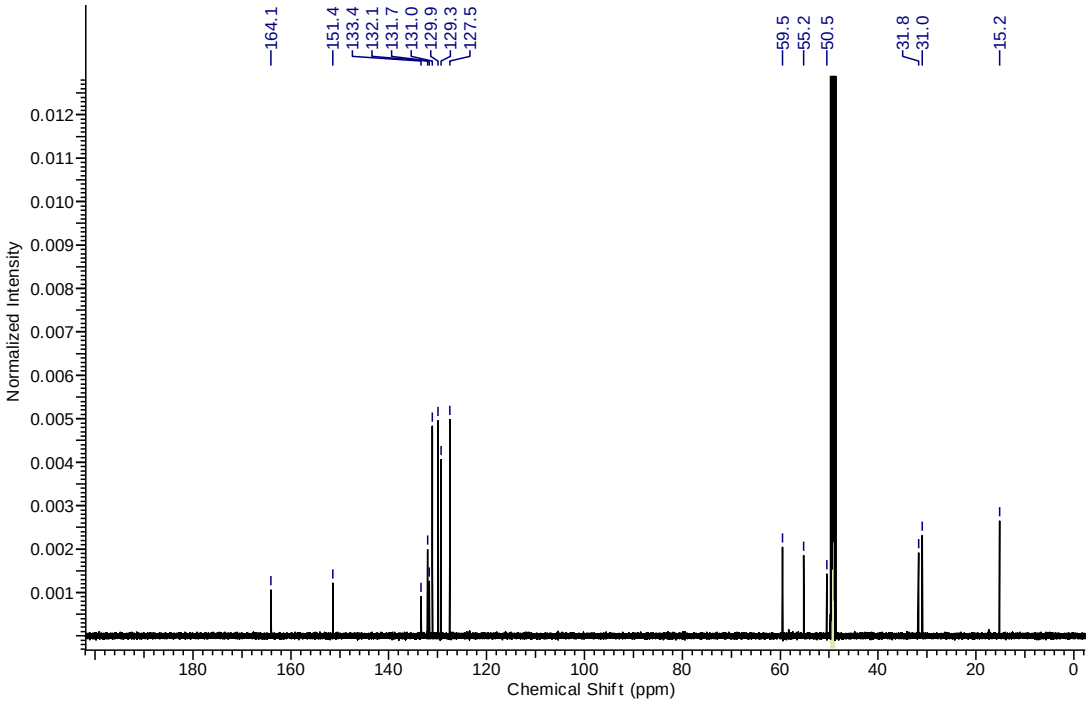




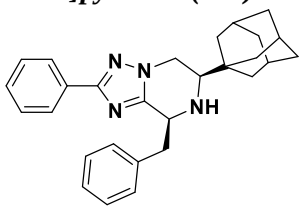
(6R,8S)-8-(2-(methylthio)ethyl)-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (148)

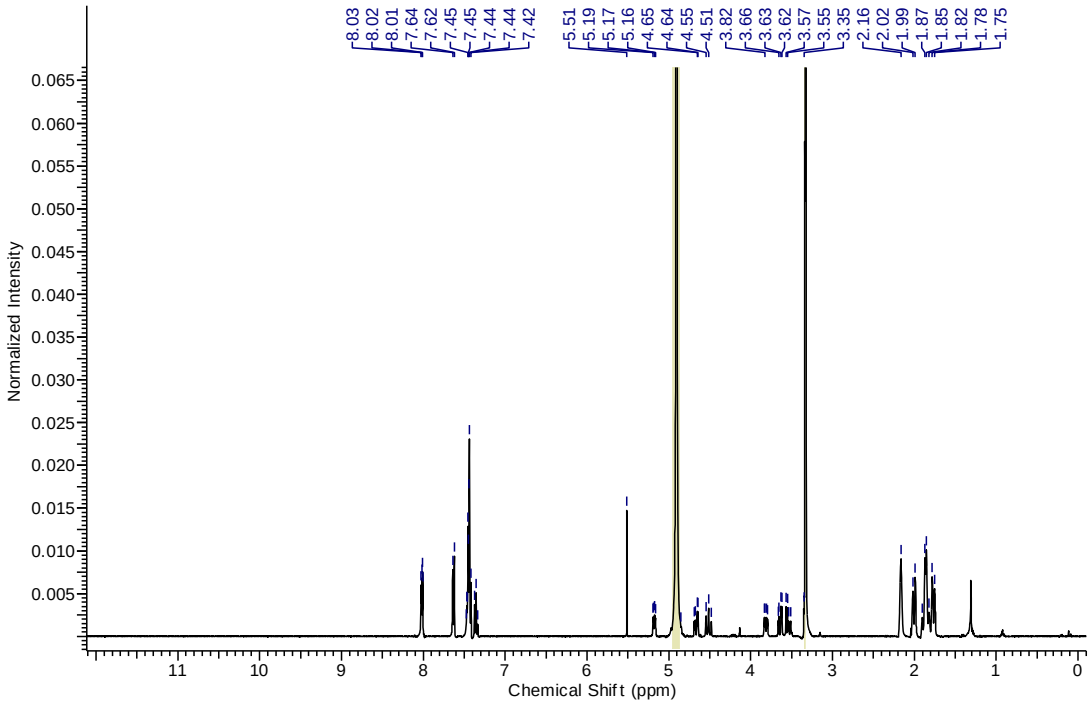


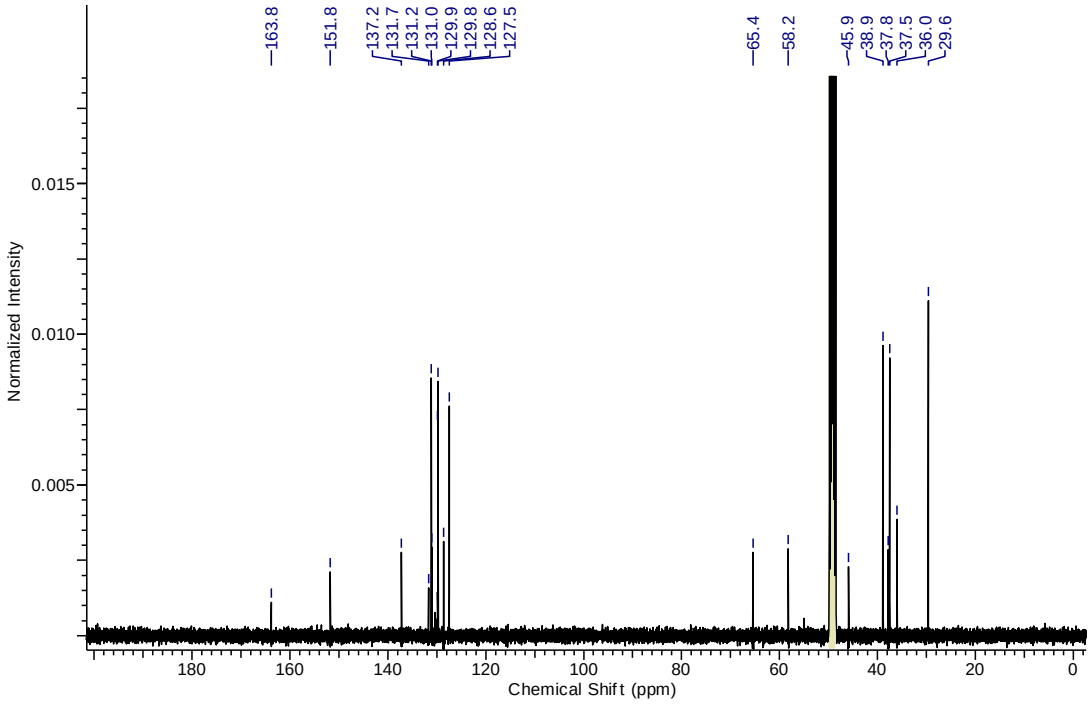




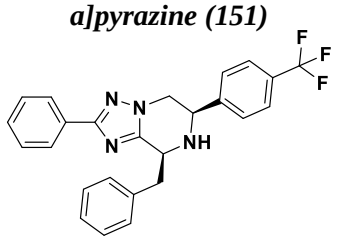
(6R,8S)-6-((1r,3R)-adamantan-1-yl)-8-benzyl-2-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (149)

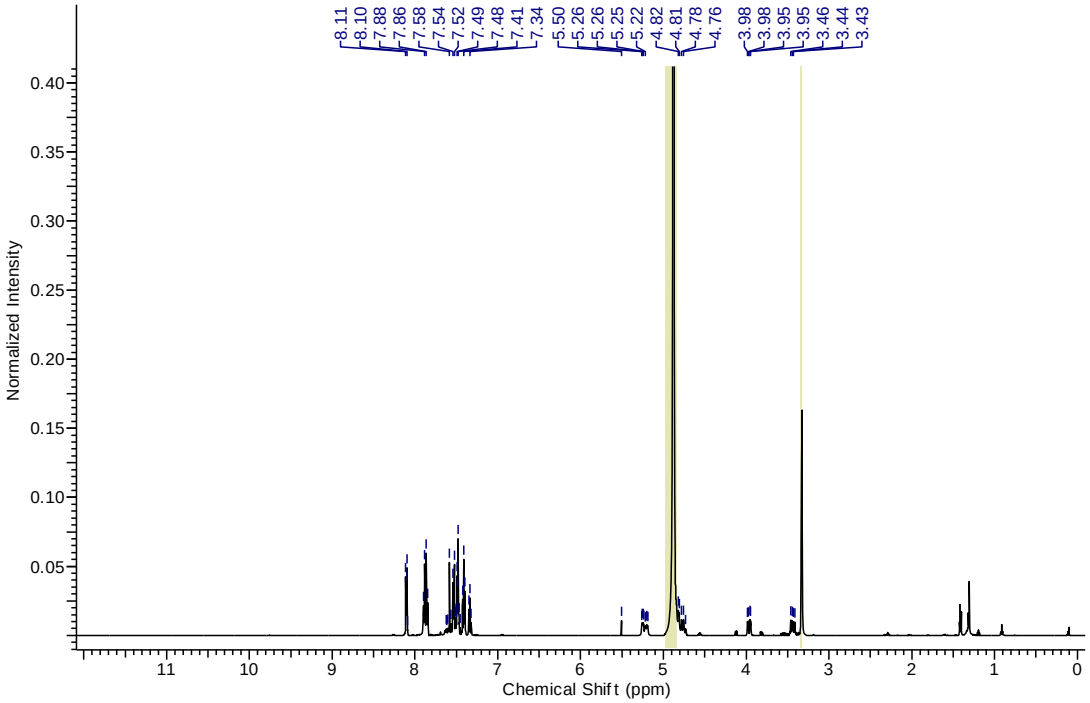


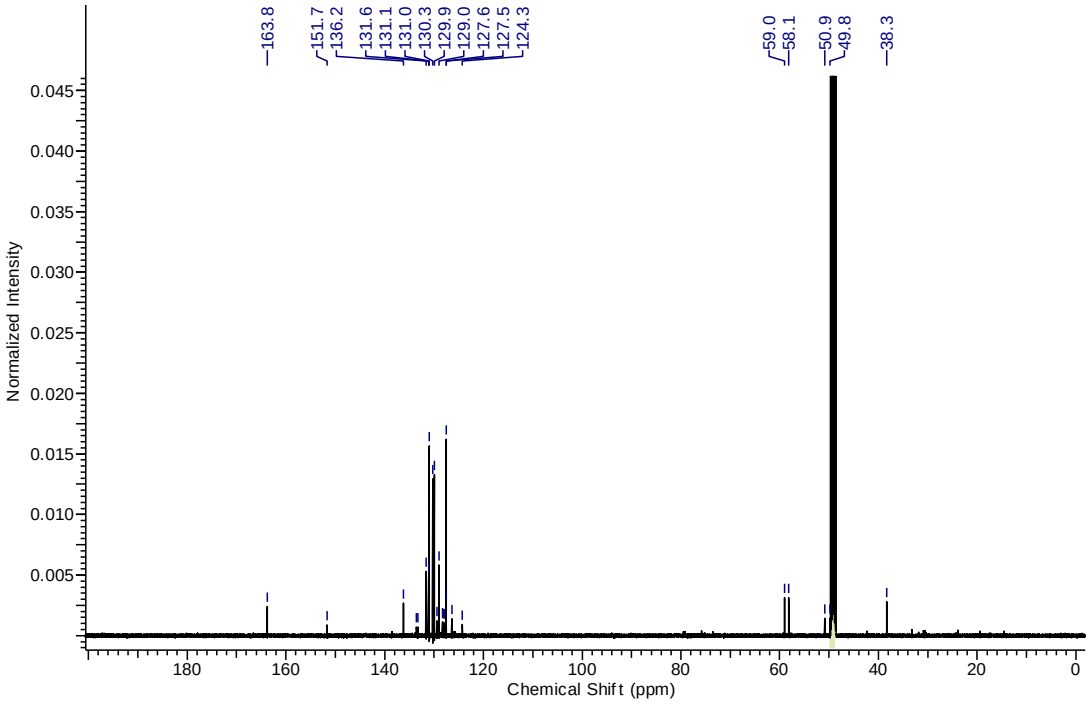




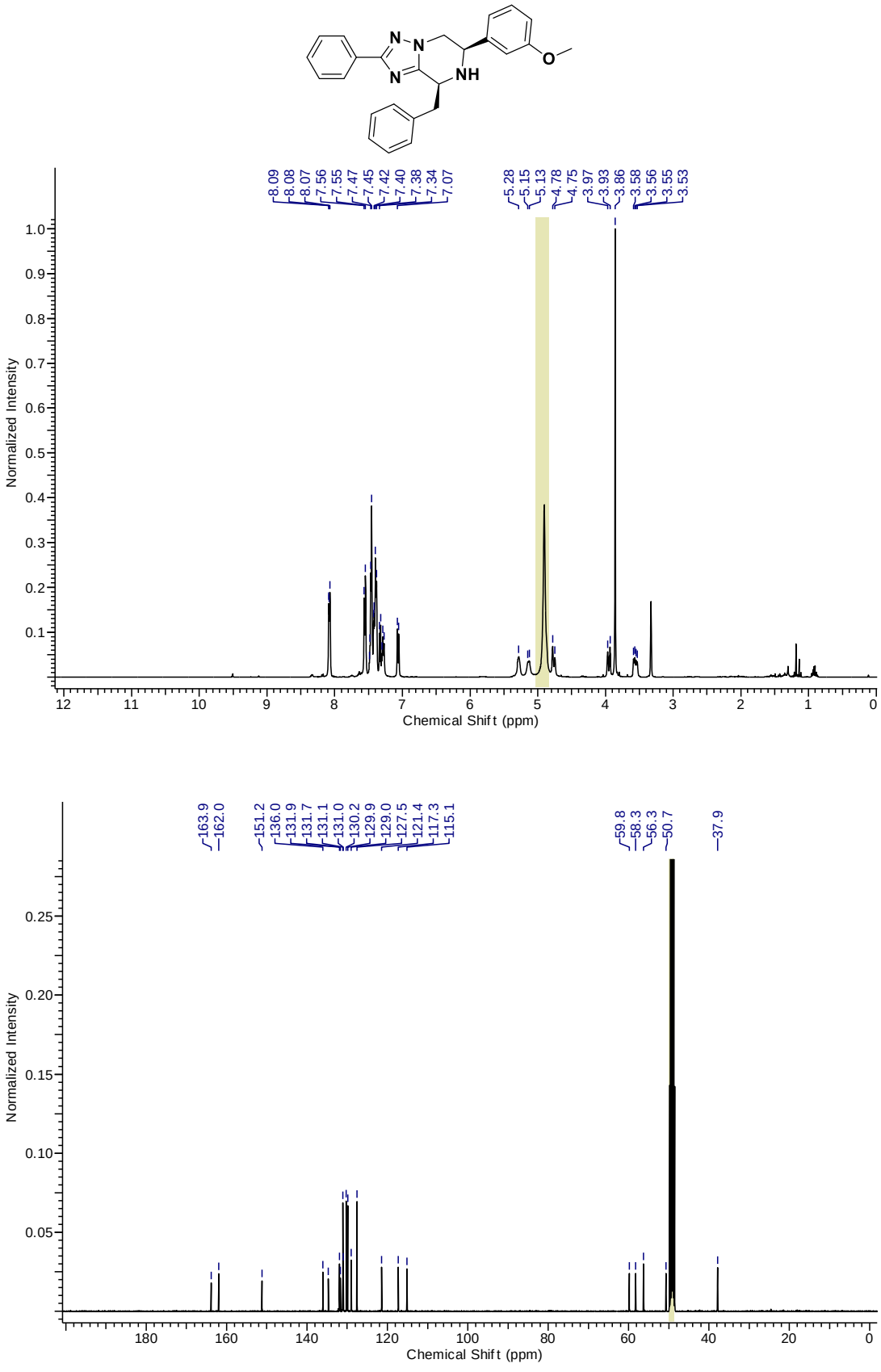
(6R,8S)-8-benzyl-2-phenyl-6-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (151)



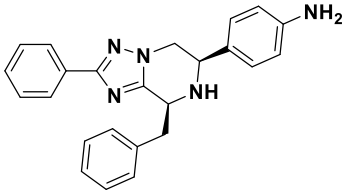


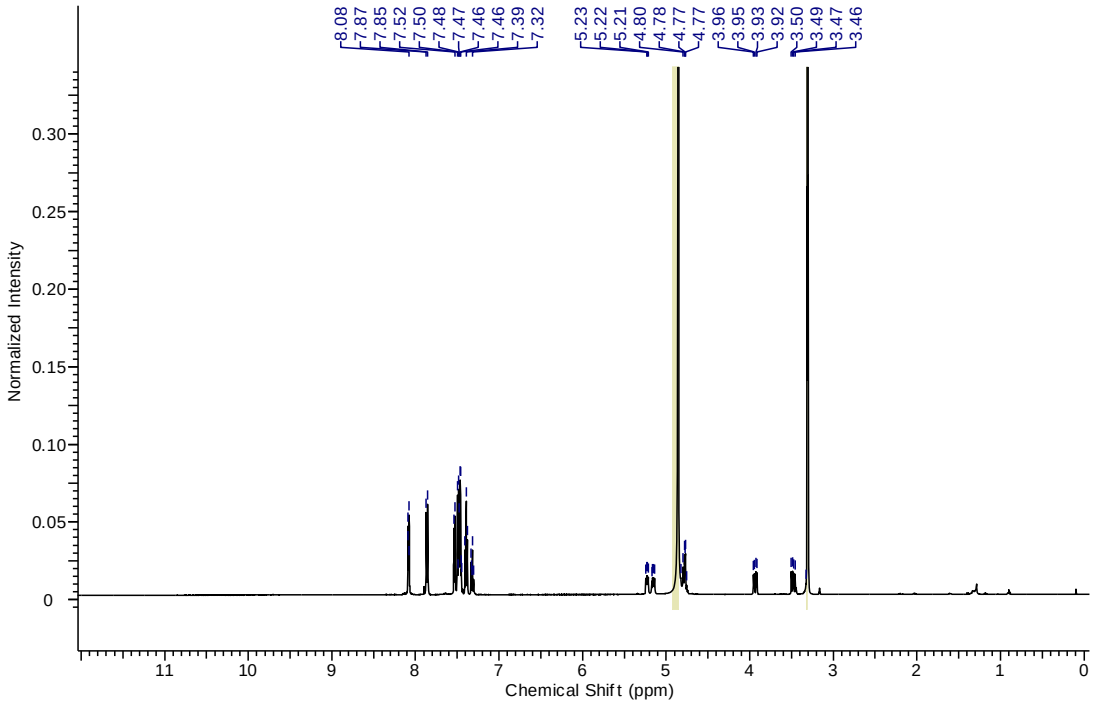


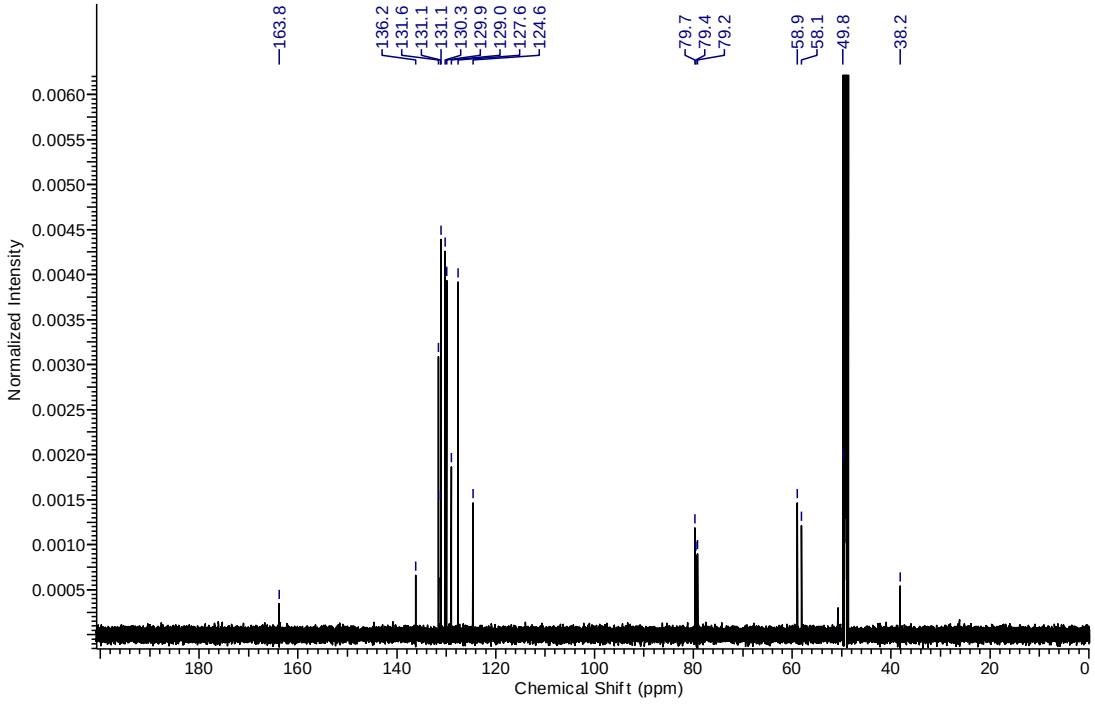
(6R,8S)-8-benzyl-6-(3-methoxyphenyl)-2-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (152)



4-((6R,8S)-8-benzyl-2-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)aniline (154)

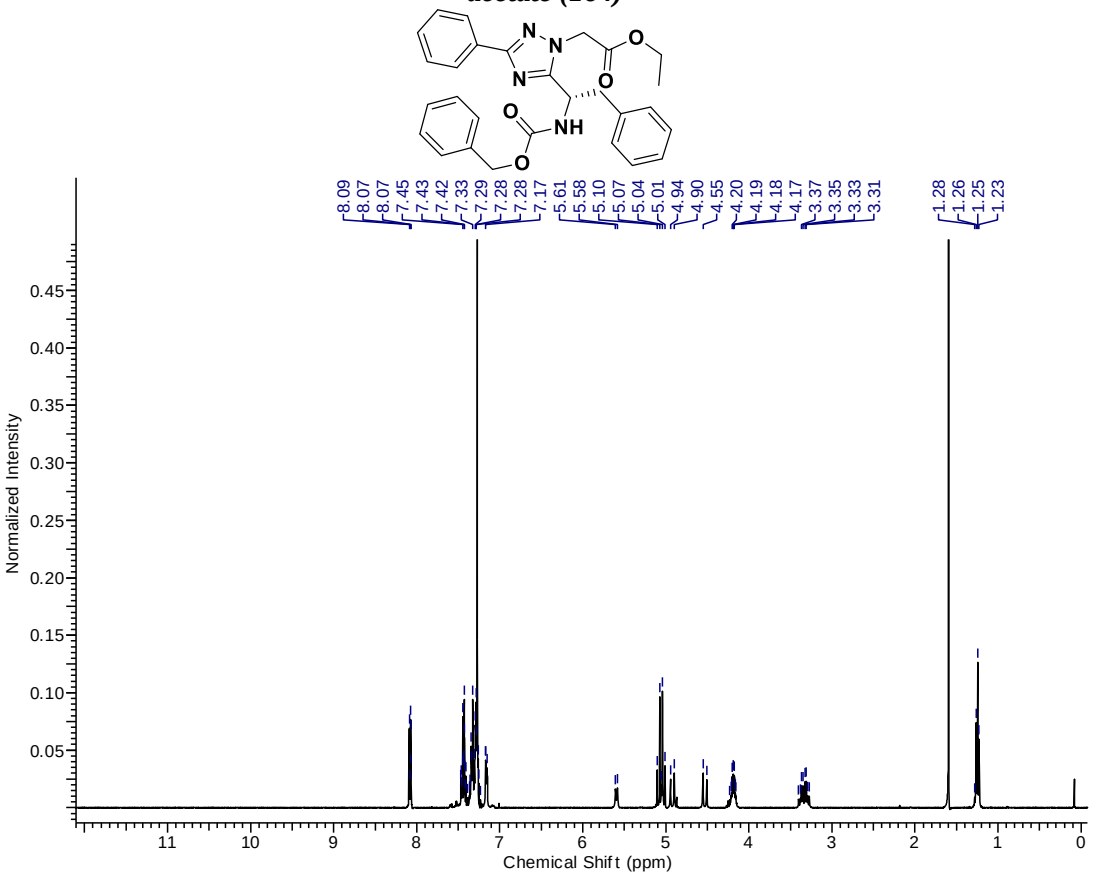


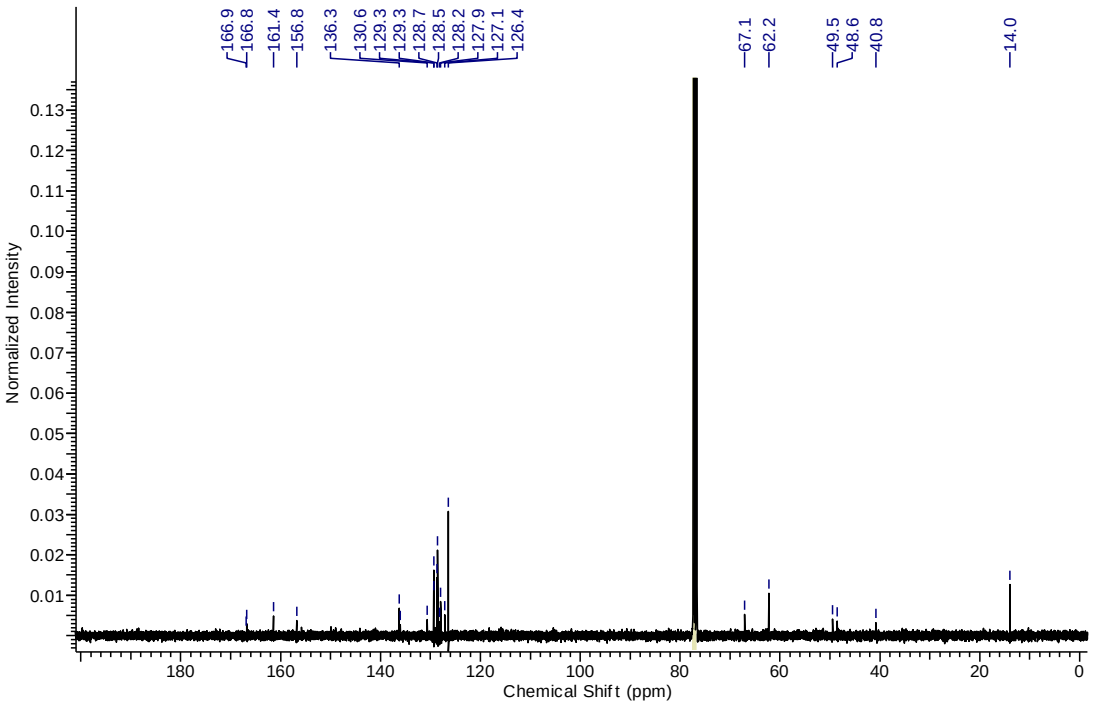




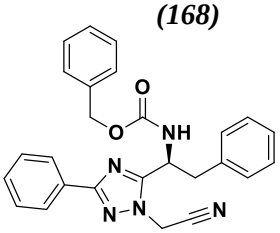
7.2.2. Efficient Synthesis of cis-1,2,4-Triazole heterocycle

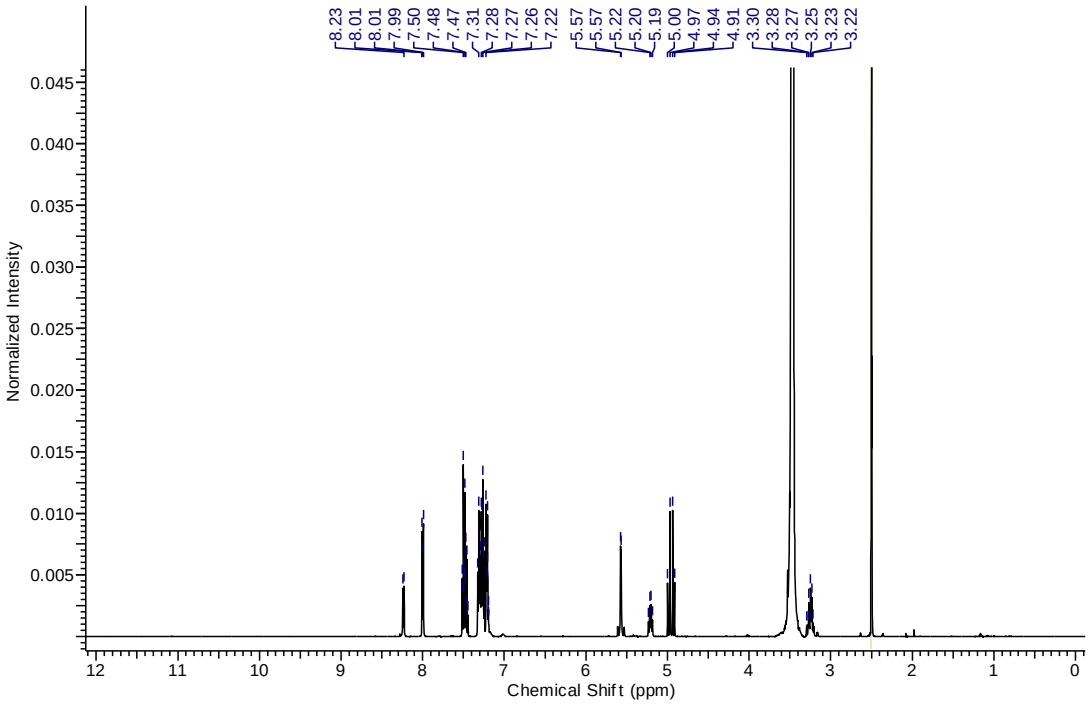
Ethyl (S)-2-(5-(1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-1-yl) acetate (164)

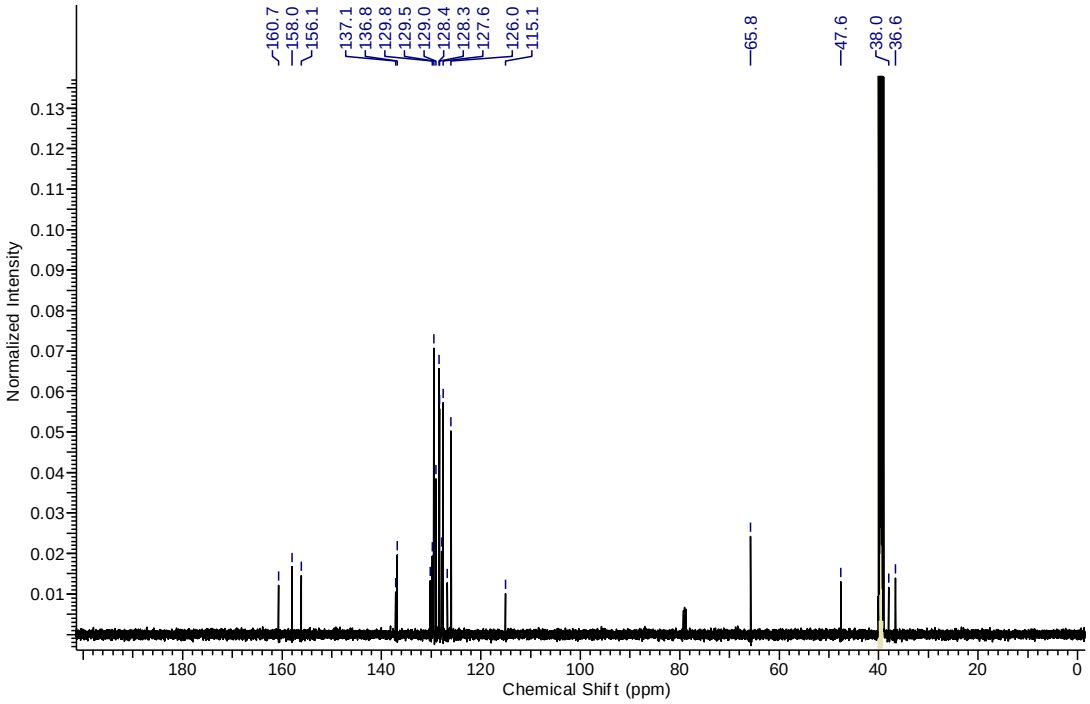




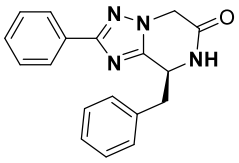
Benzyl (S)-(1-(1-(cyanomethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (168)

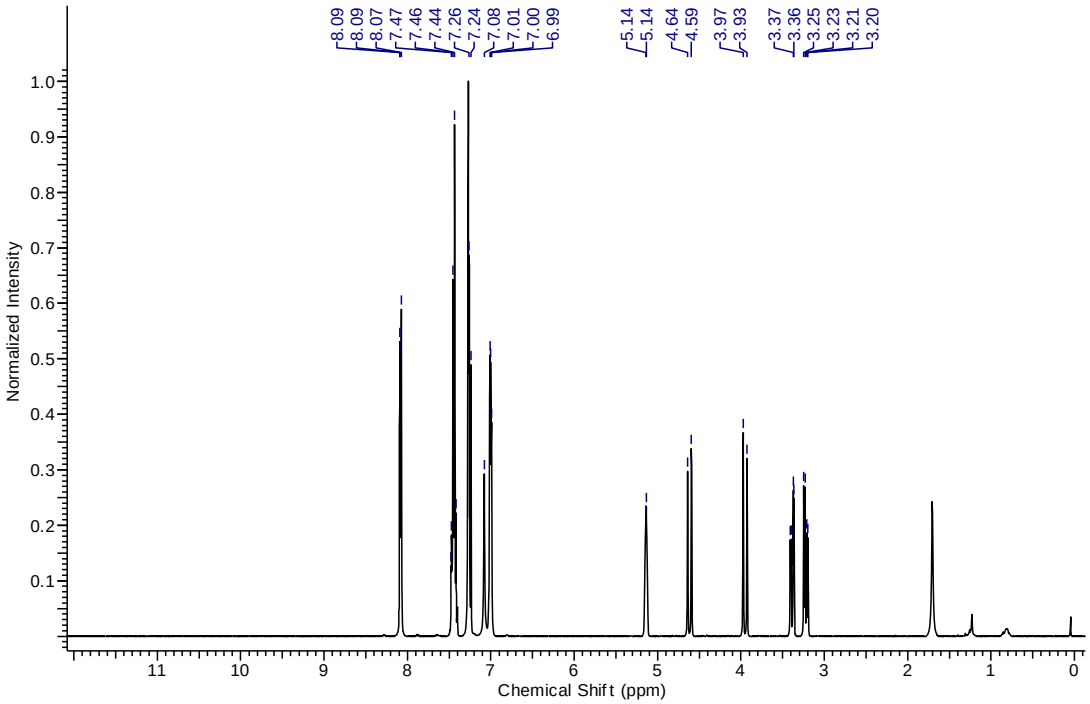


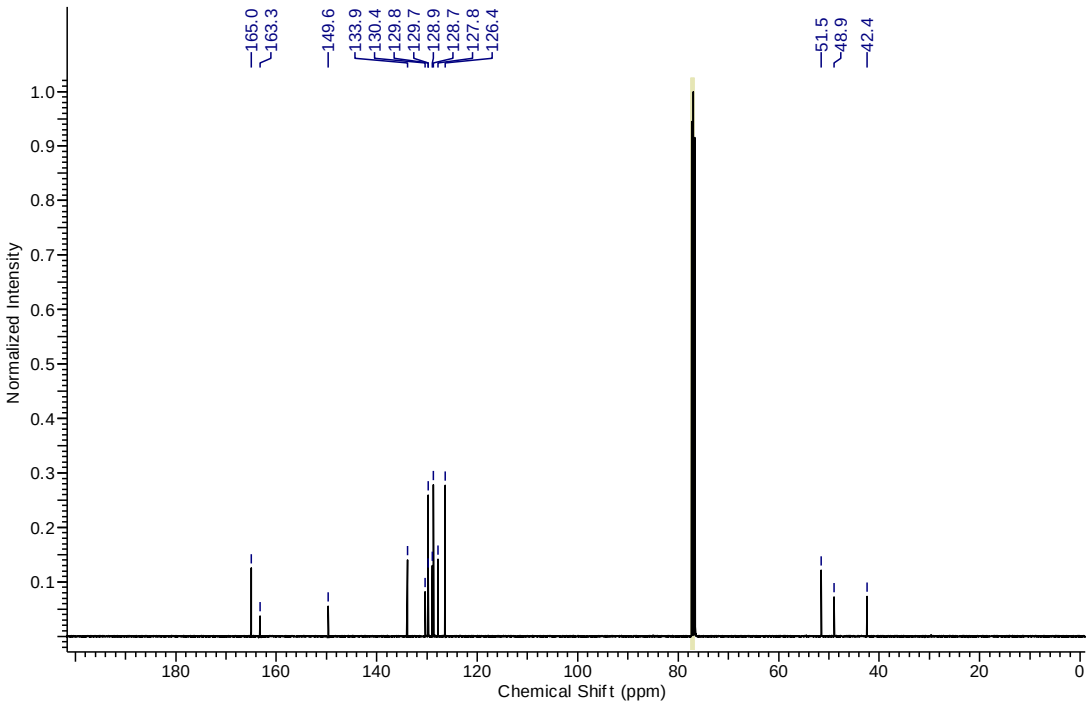




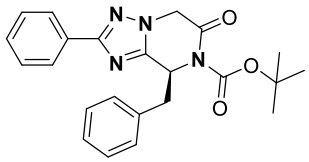
(S)-8-benzyl-2-phenyl-7,8-dihydro-[1,2,4]triazolo[1,5-a]pyrazin-6(5H)-one (167)

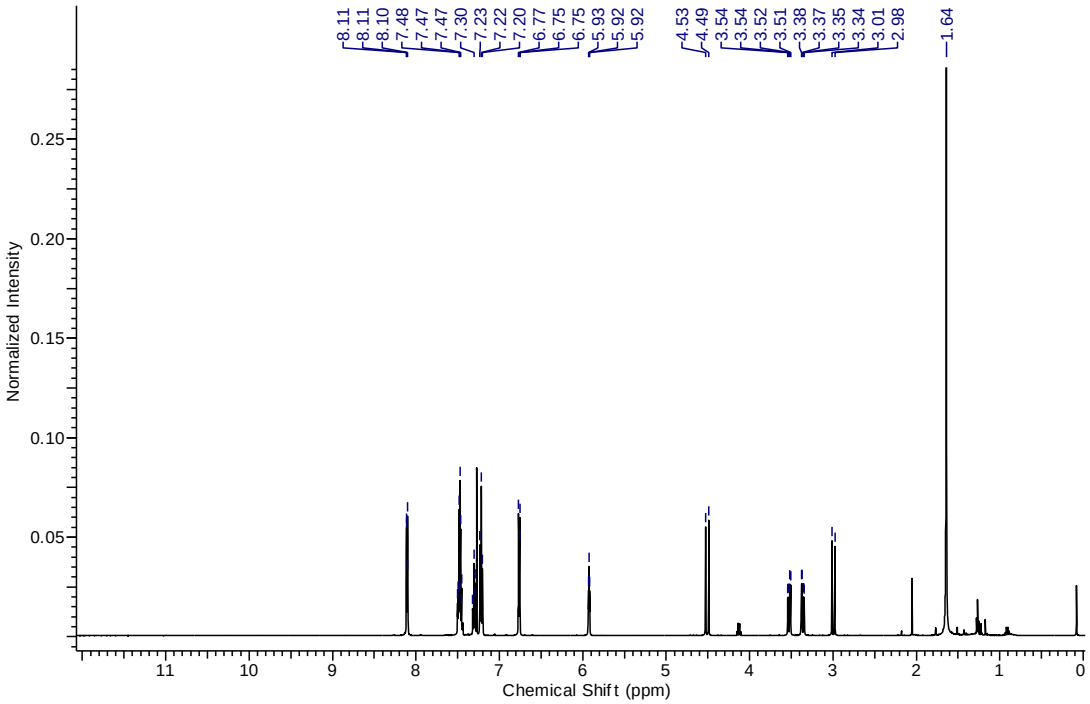


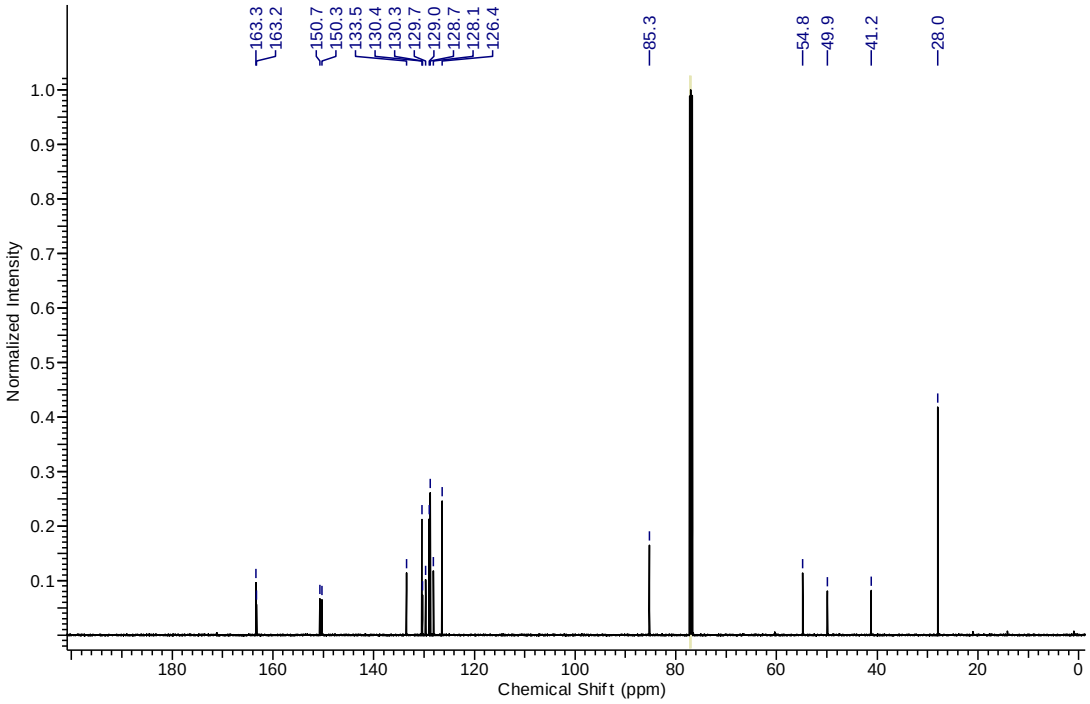




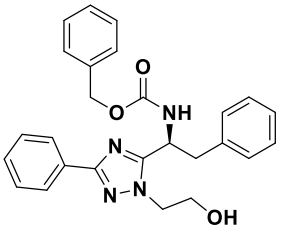
tert-butyl (S)-8-benzyl-6-oxo-2-phenyl-5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazine-7(8H)-carboxylate (170)

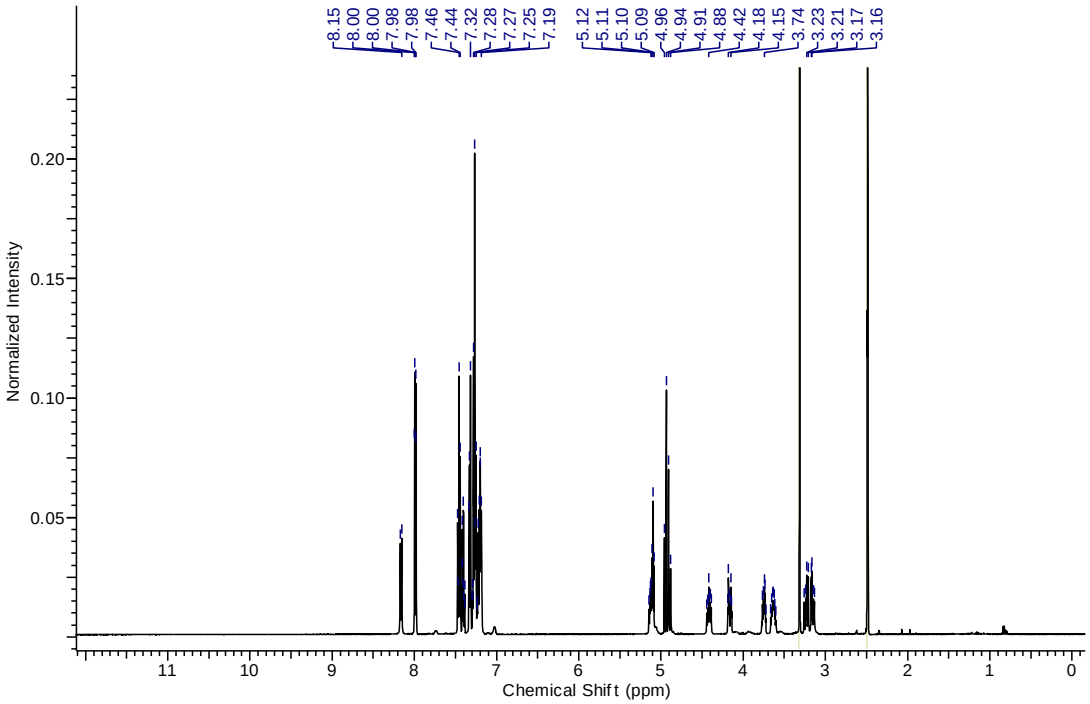


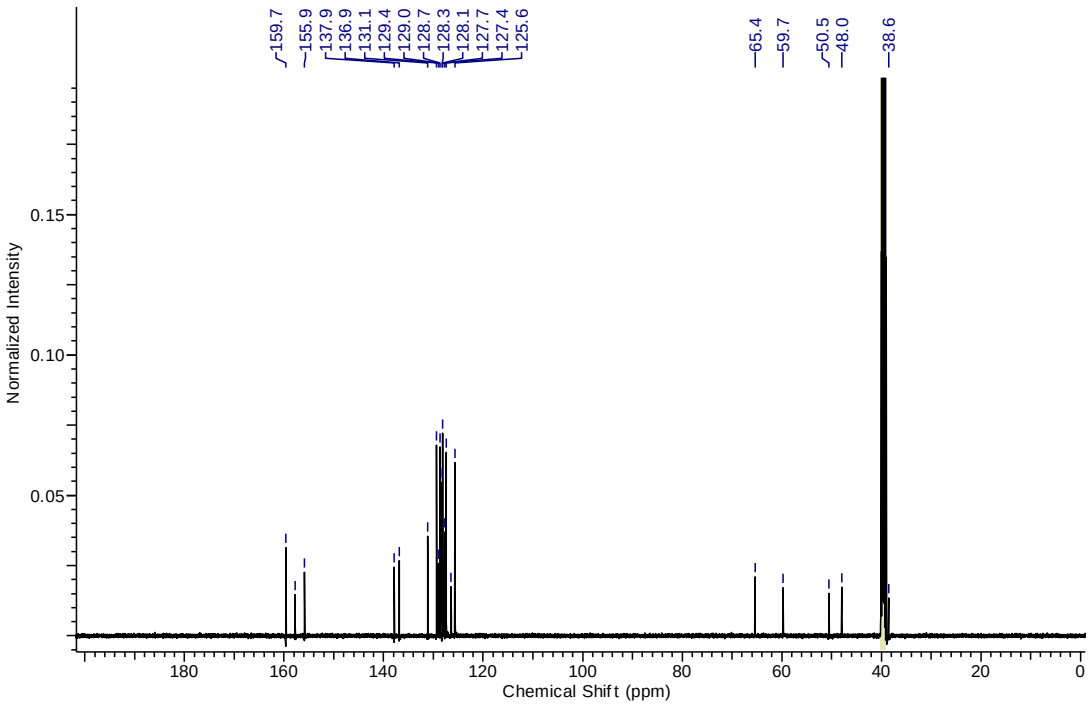




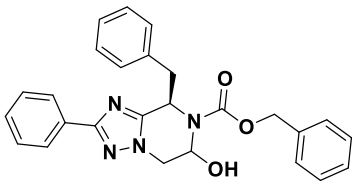
Benzyl (S)-(1-(1-(2-hydroxyethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate (174)

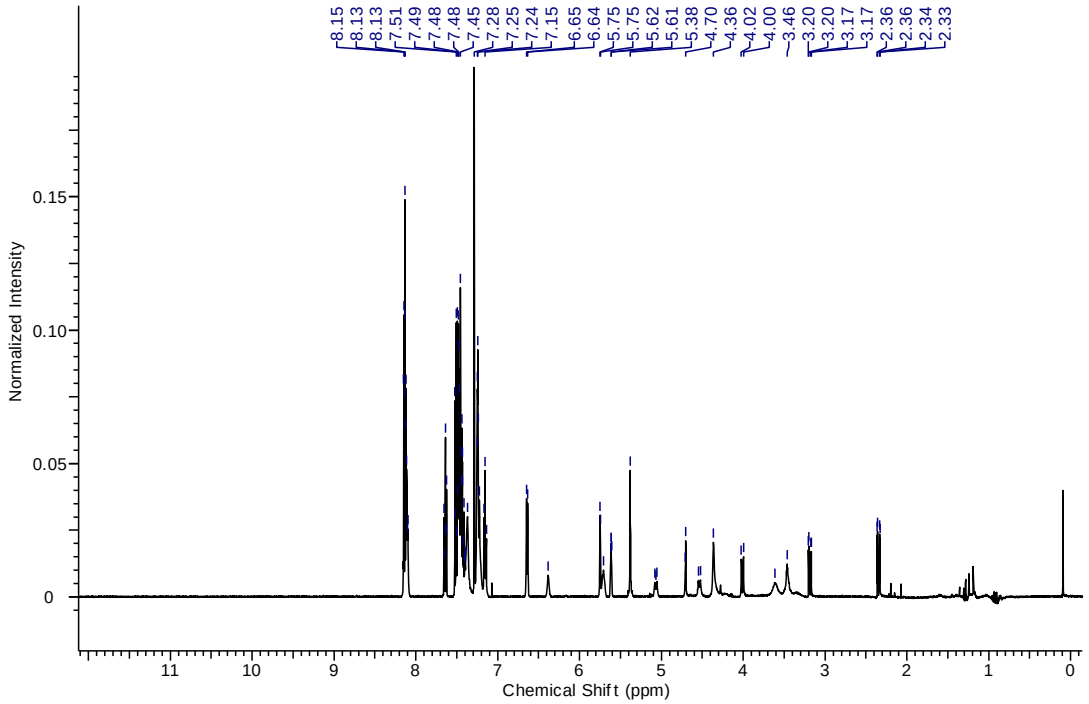


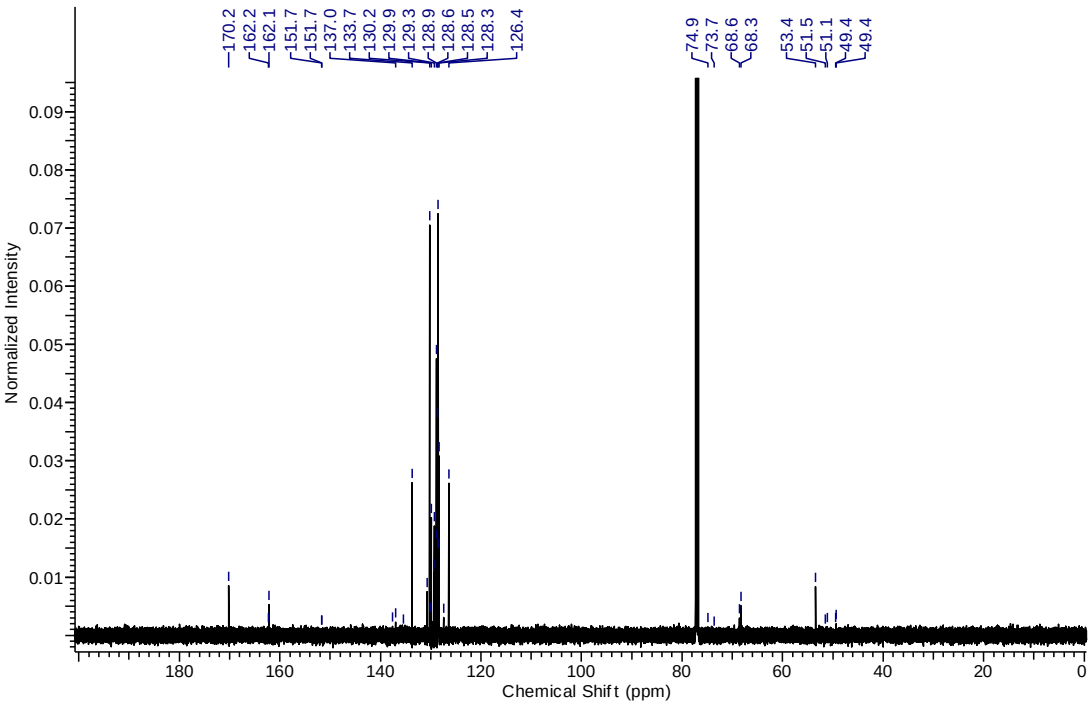




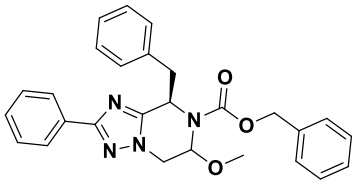
Benzyl 8-benzyl-6-hydroxy-2-phenyl-5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazine-7(8H)-carboxylate (175)

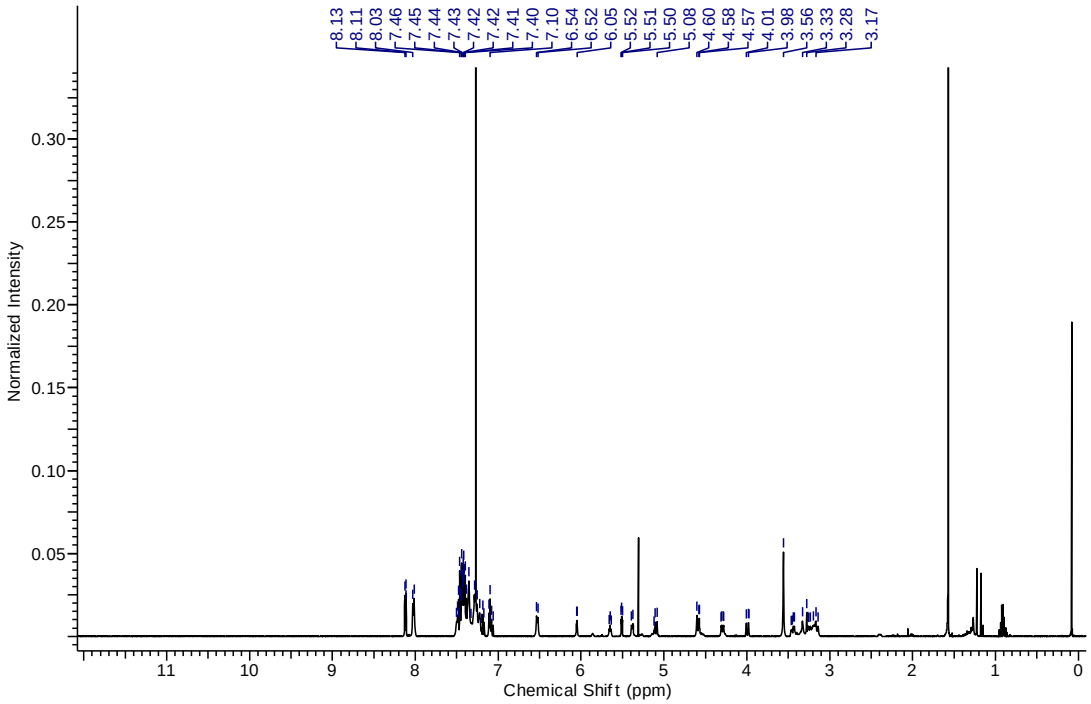


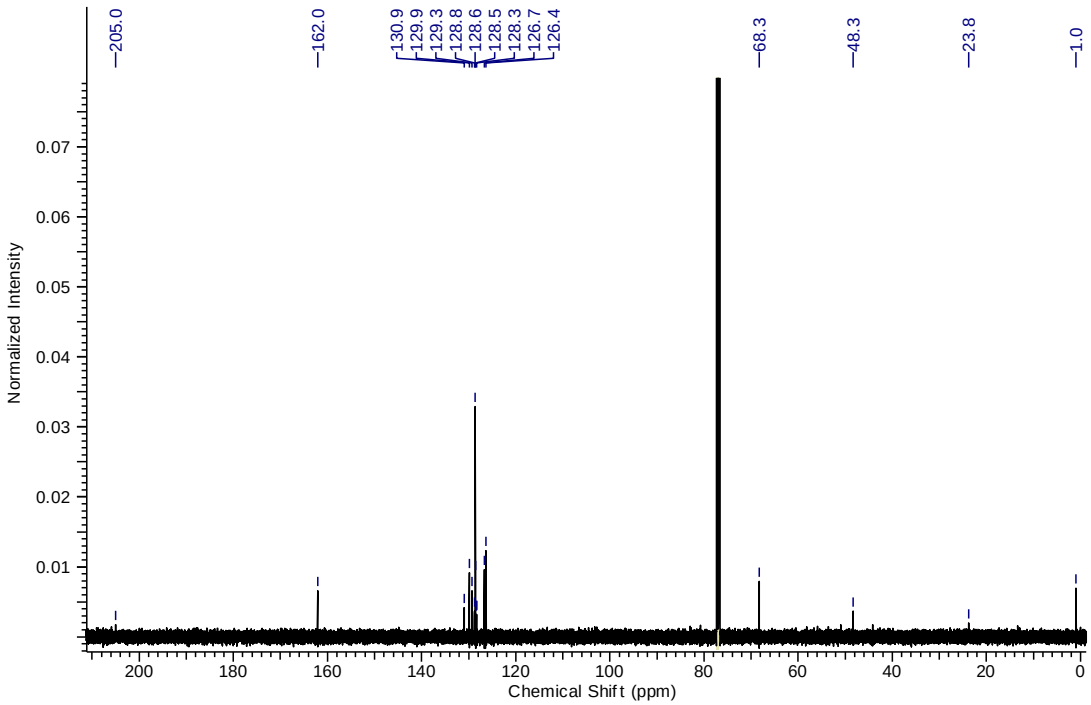




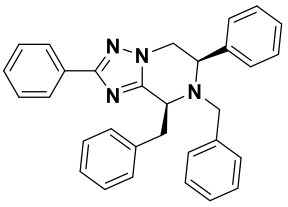
Benzyl 8-benzyl-6-methoxy-2-phenyl-5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazine-7(8H)-carboxylate (177)

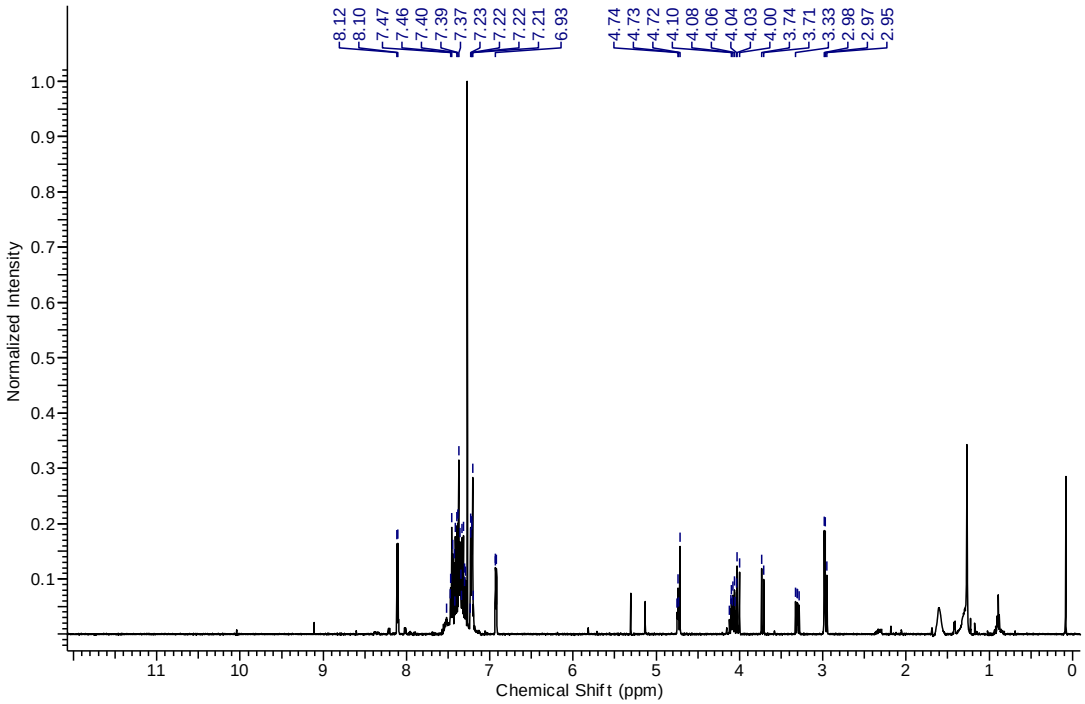


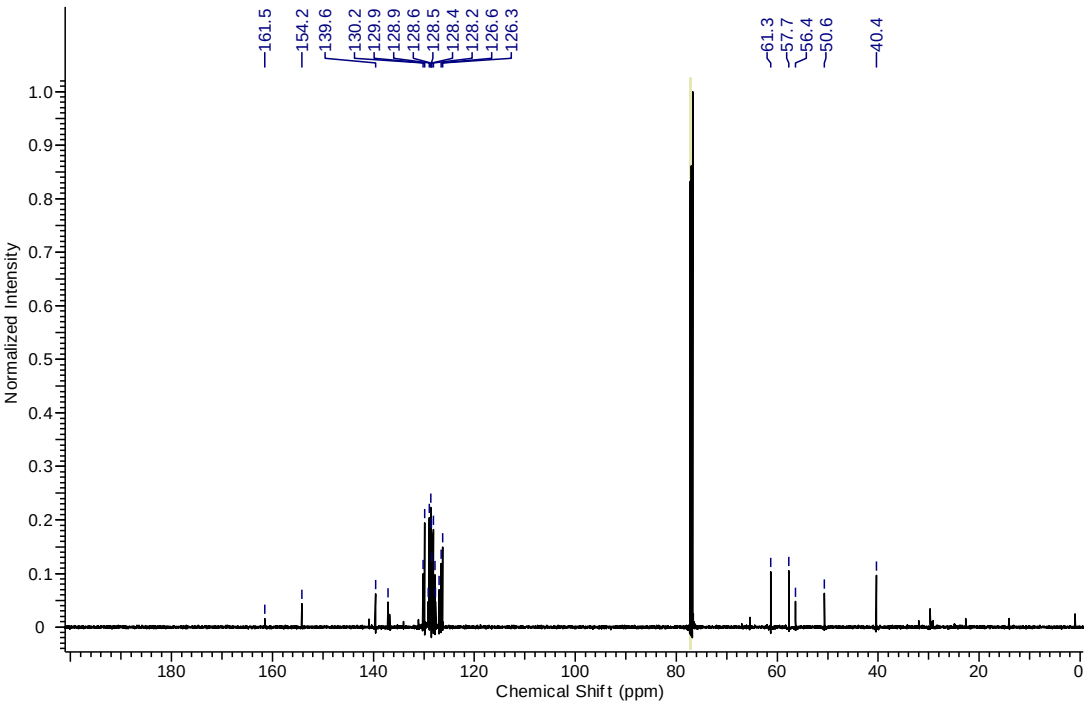




(6R,8S)-7,8-dibenzyl-2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (180)

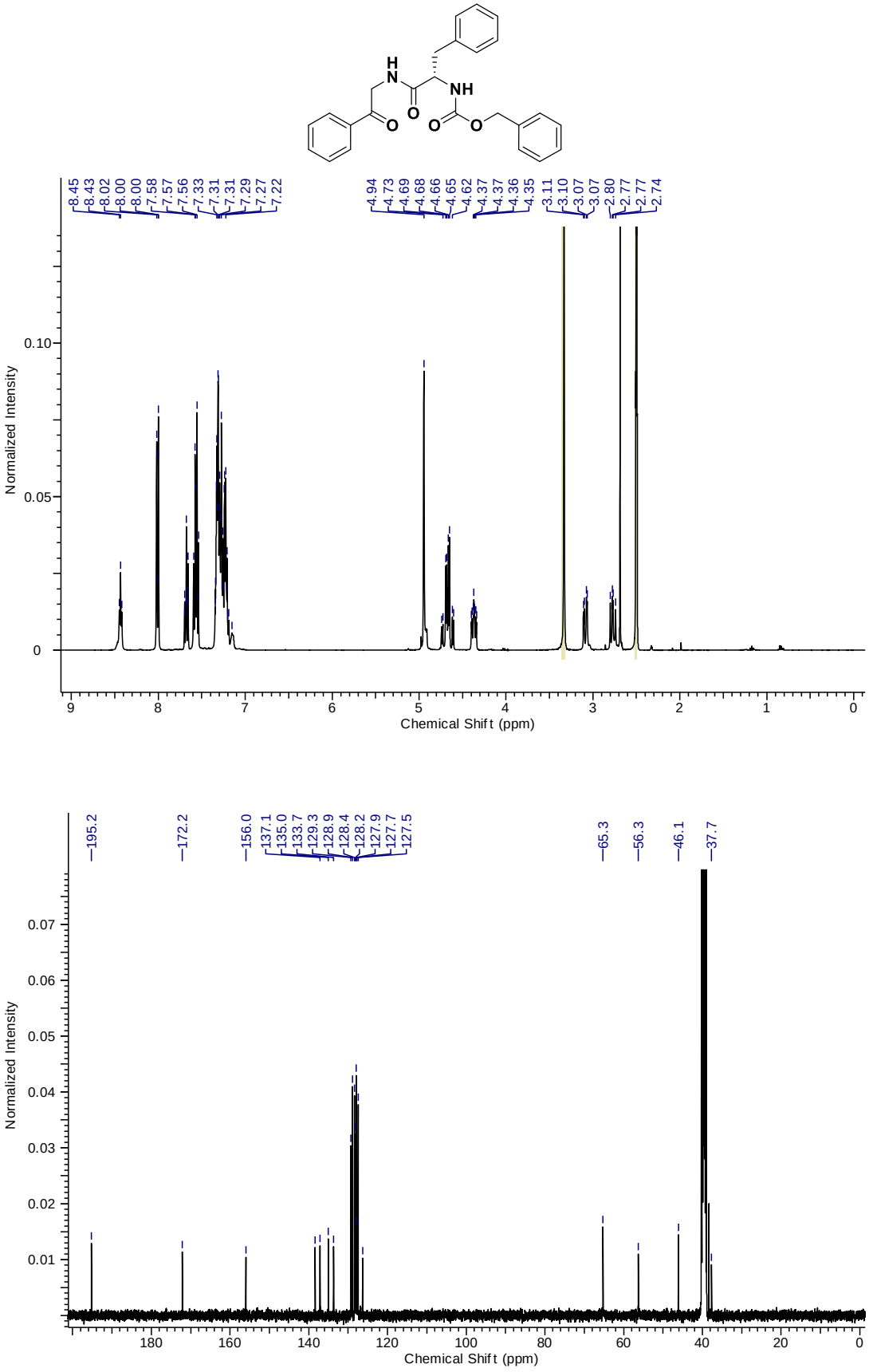




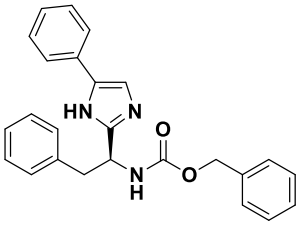


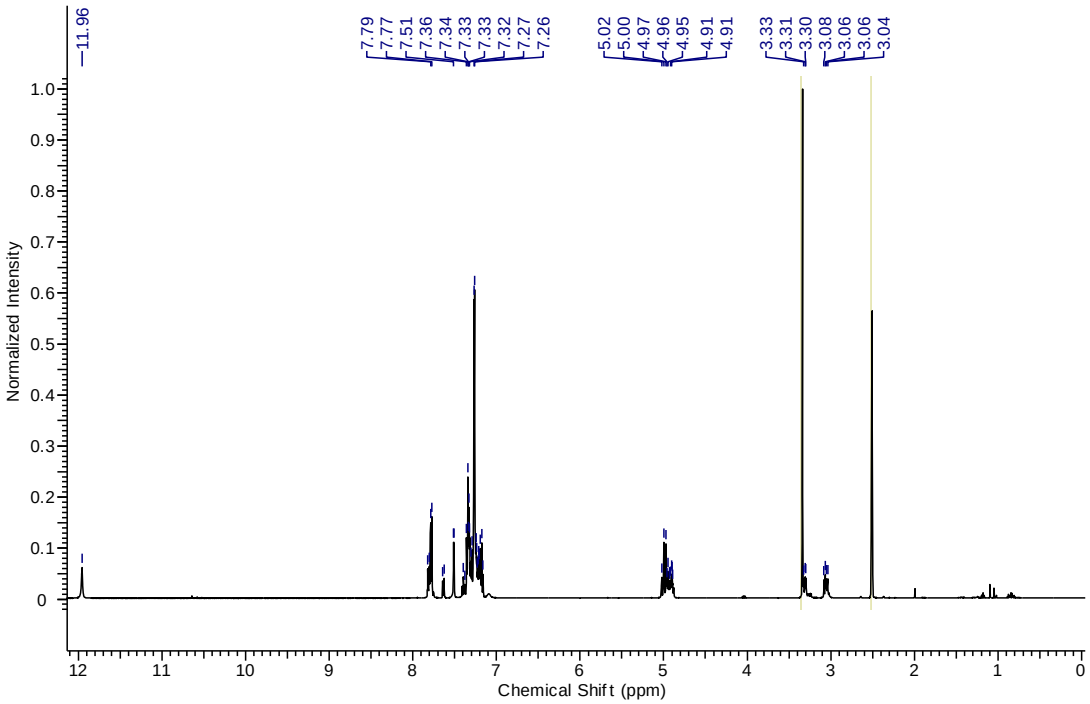
7.2.3. Efficient Synthesis of 1,3-Imidazole Heterocycles

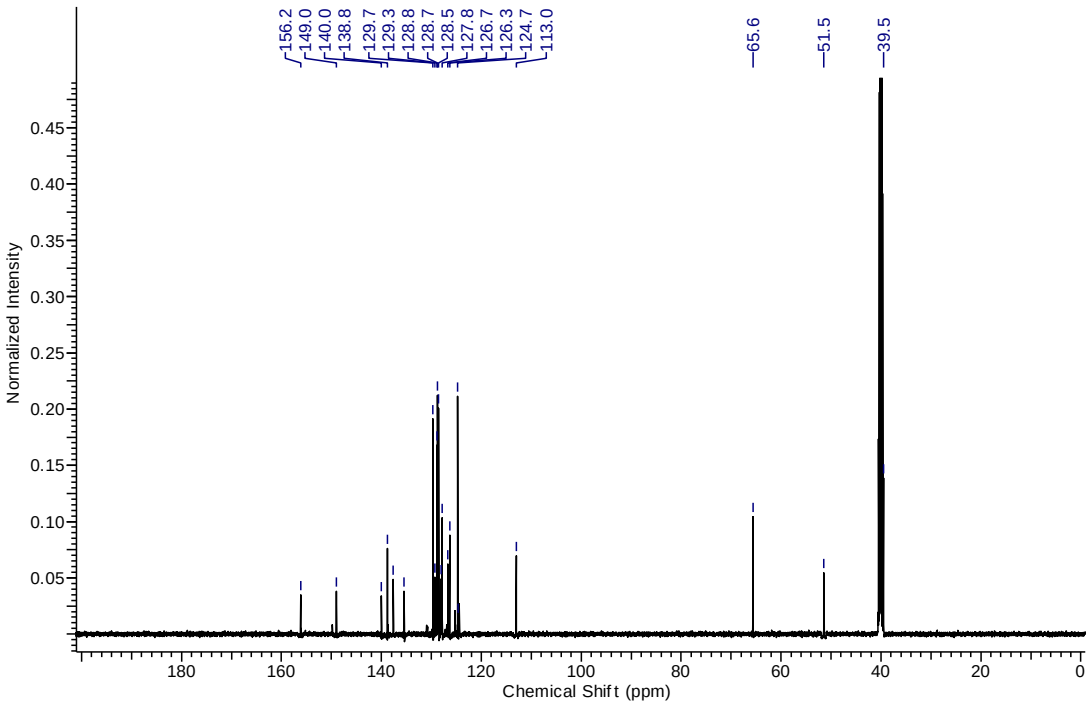
Benzyl (S)-(1-oxo-1-((2-oxo-2-phenylethyl)amino)-3-phenylpropan-2-yl)carbamate (192)



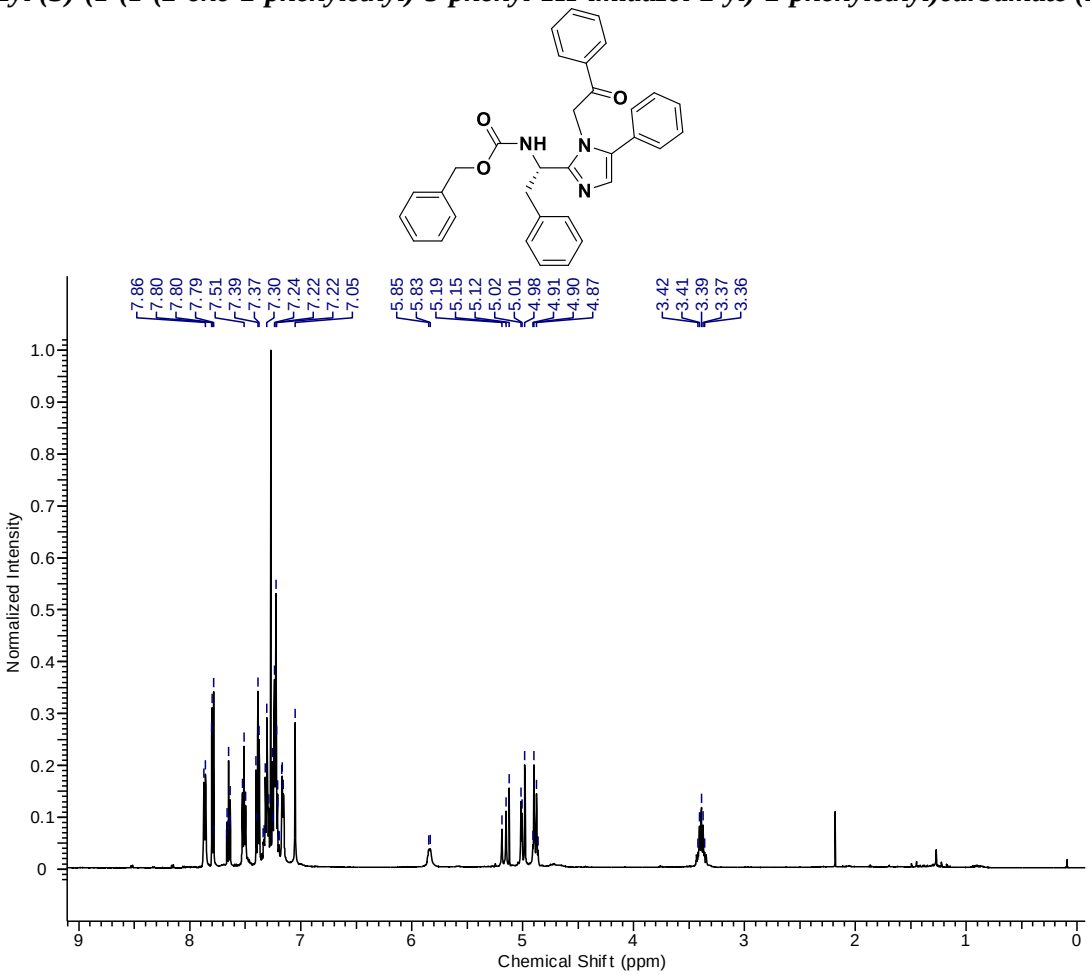
Benzyl (S)-(2-phenyl-1-(5-phenyl-1H-imidazol-2-yl)ethyl)carbamate (193)

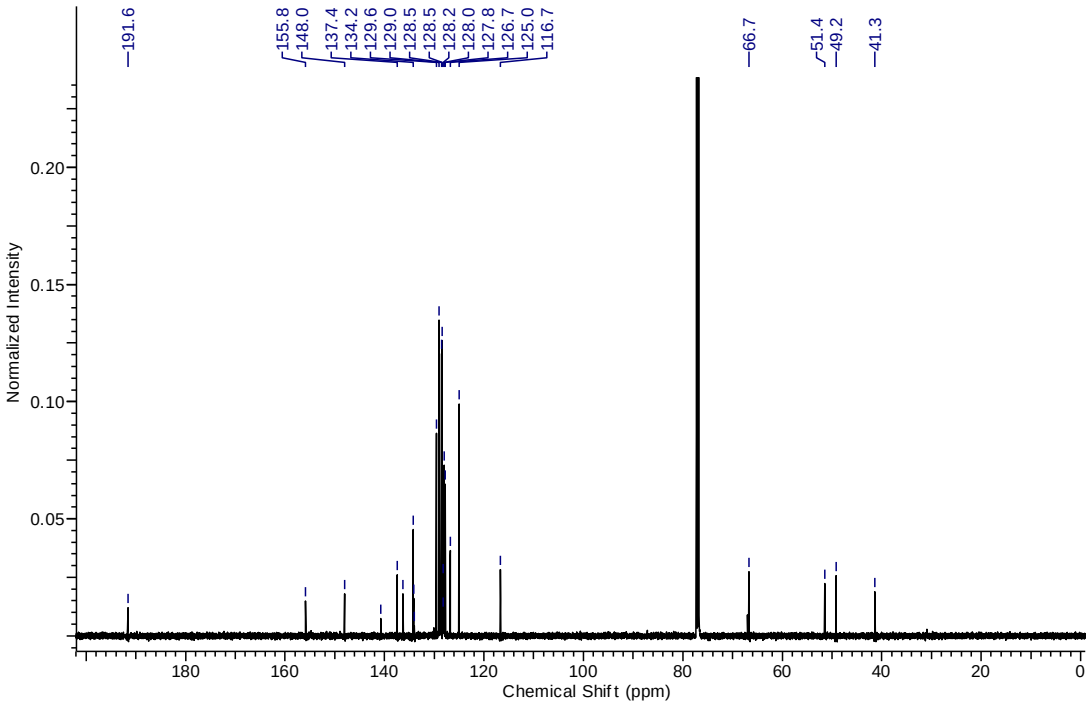




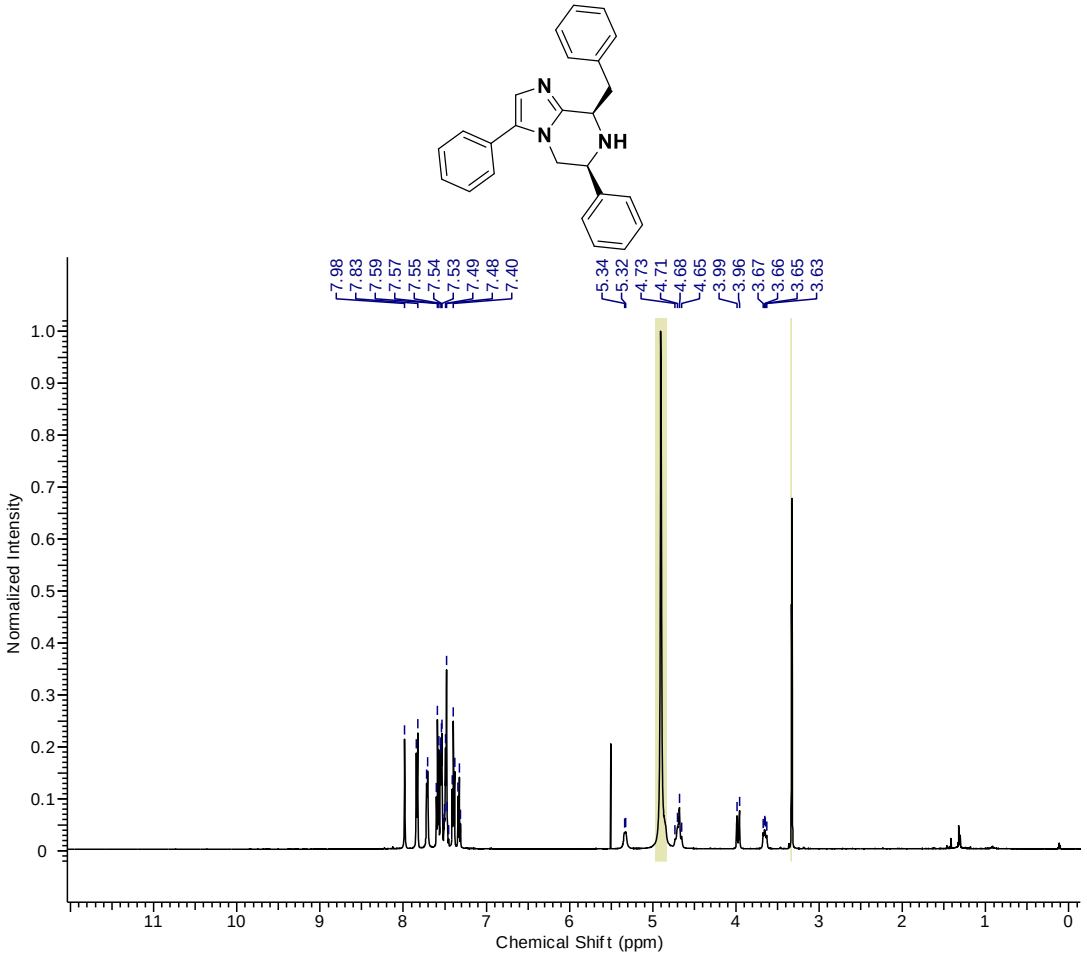


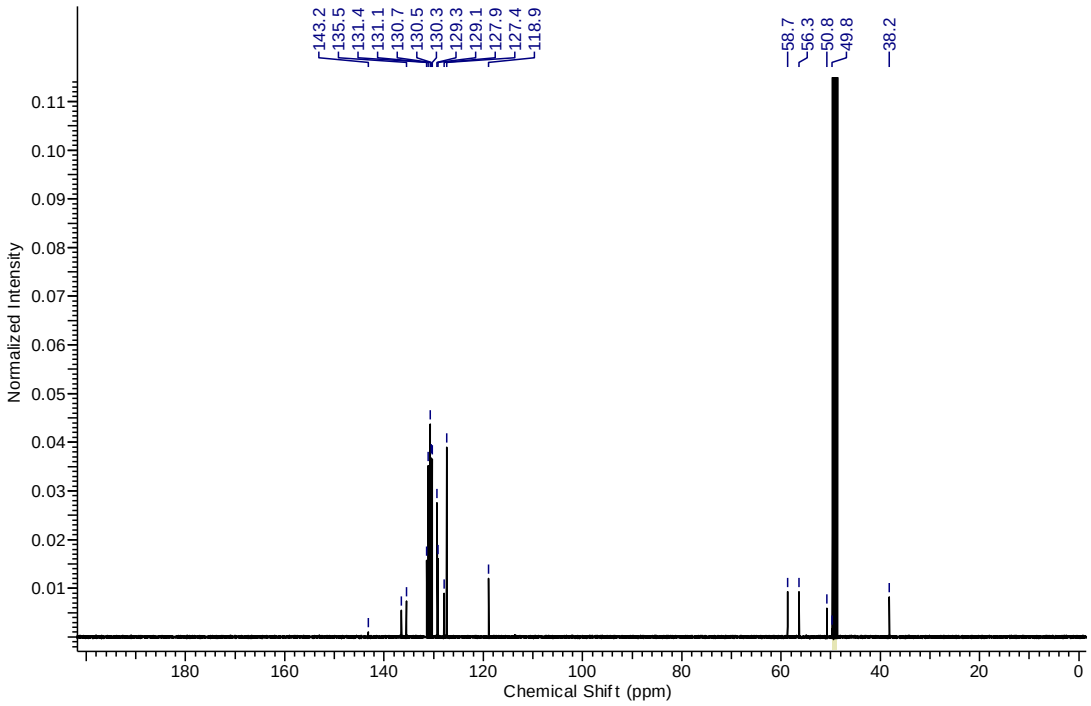
Benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-5-phenyl-1H-imidazol-2-yl)-2-phenylethyl)carbamate (194)





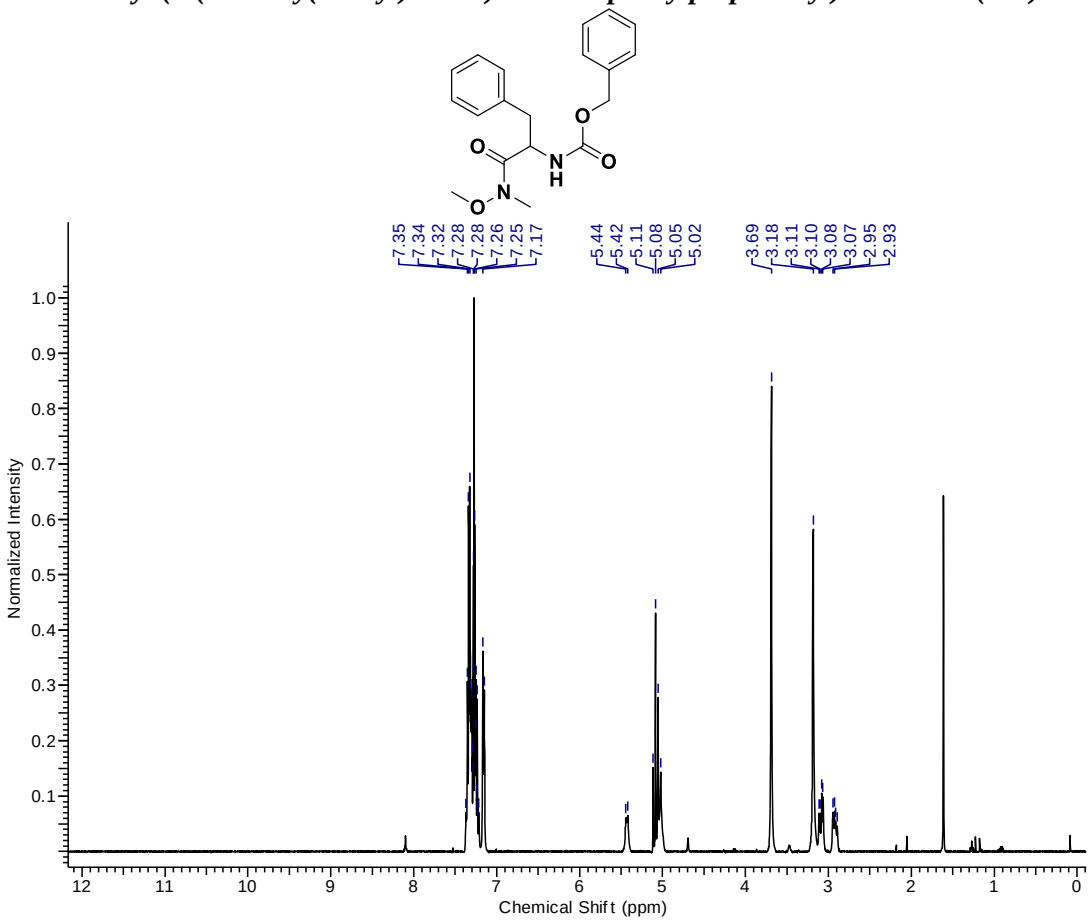
(6S,8R)-8-benzyl-3,6-diphenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine (195)

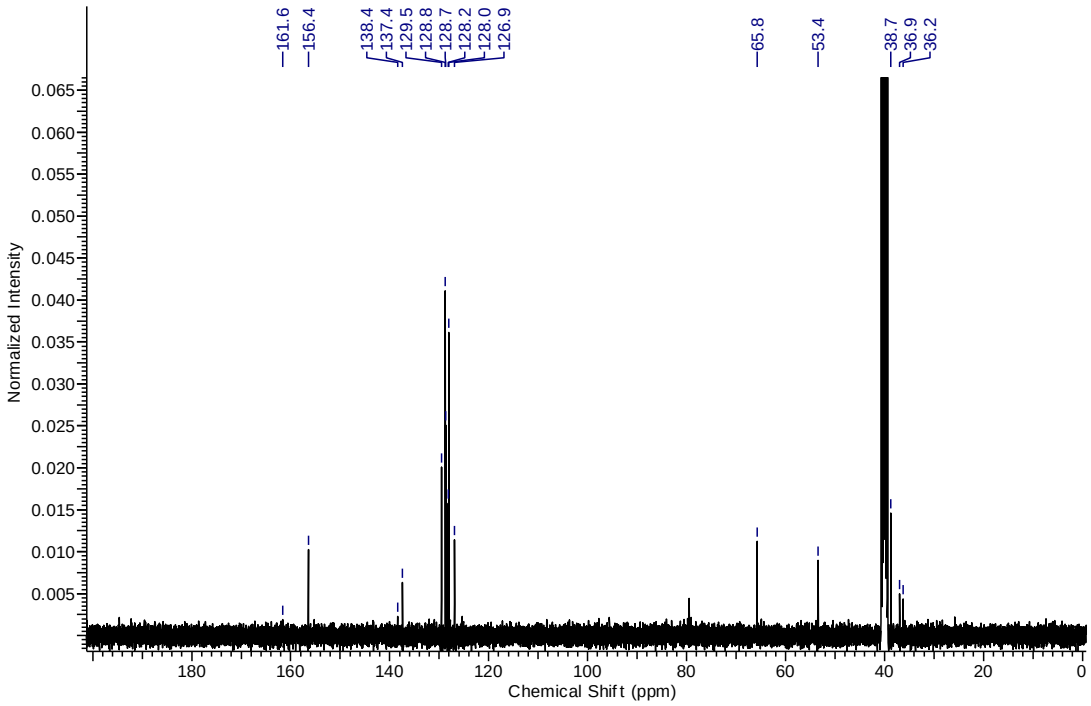




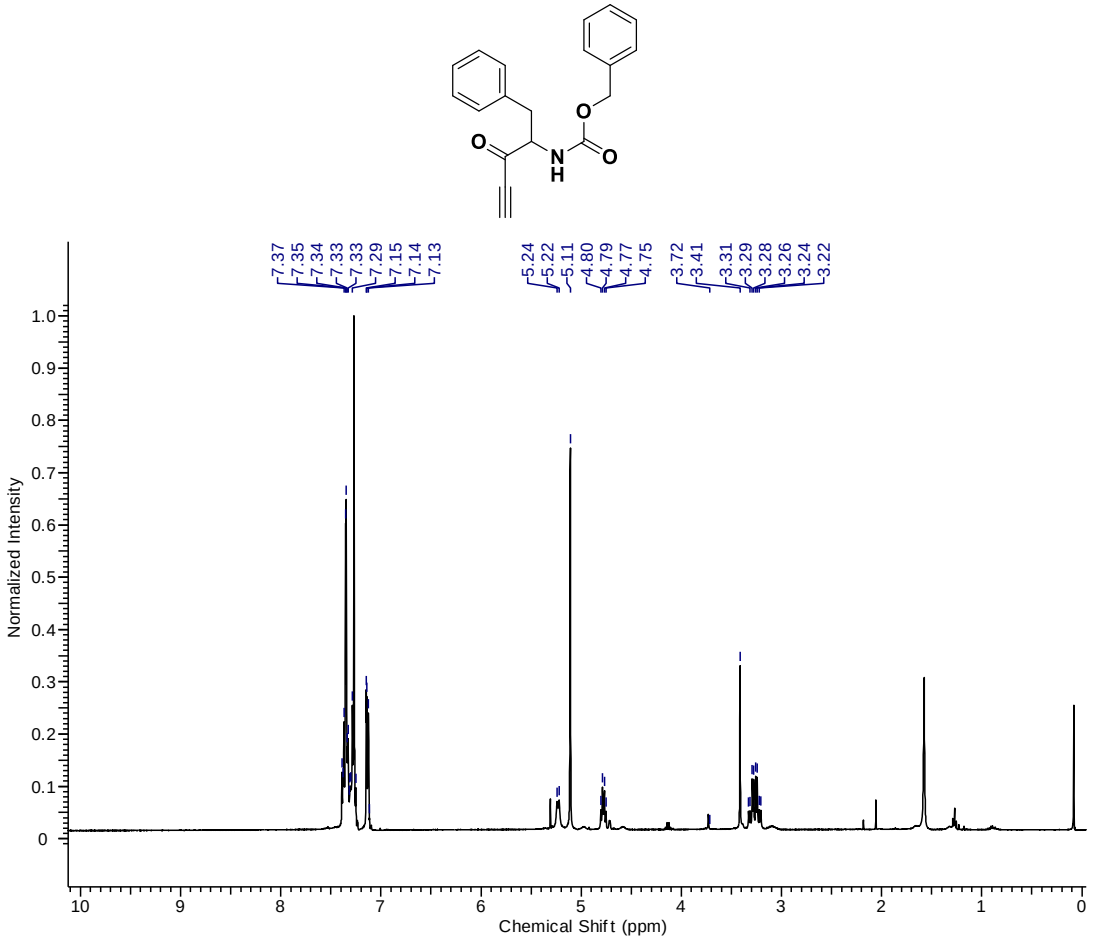
7.2.4. Efficient Synthesis of 1,2-pyrazole-based Scaffolds

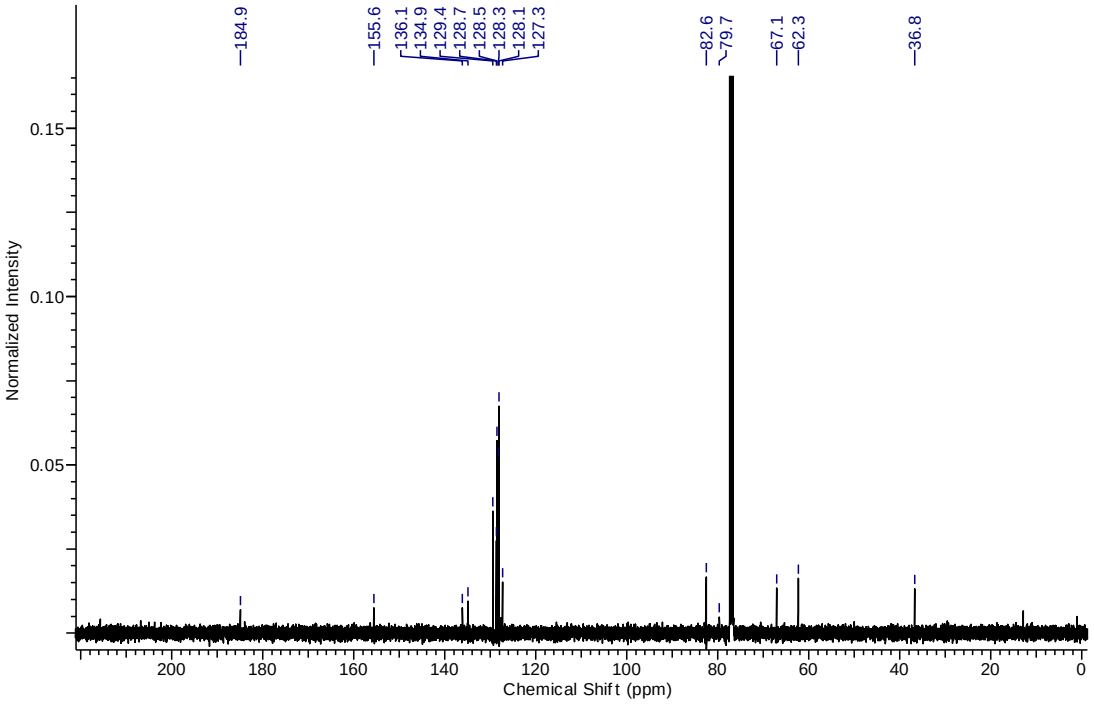
6.Benzyl (1-(methoxy(methyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (202)



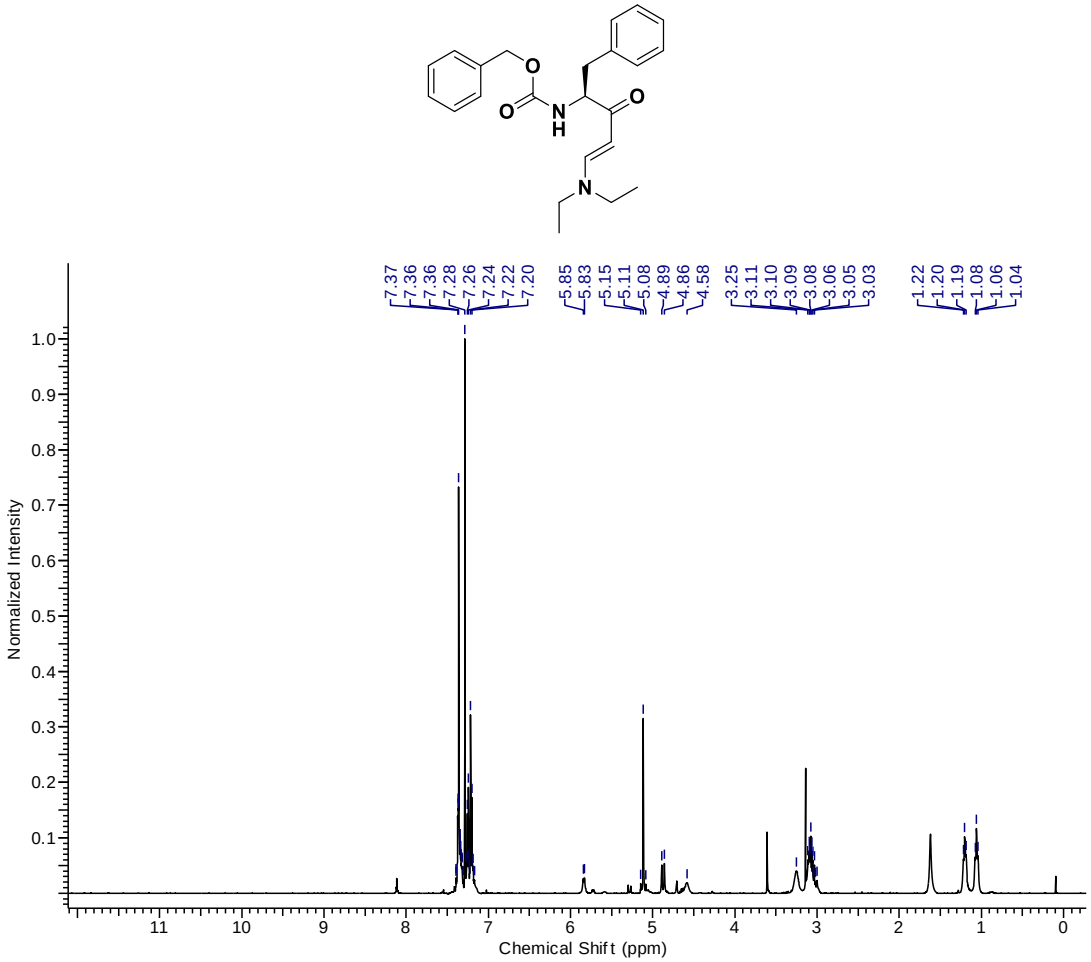


Benzyl (3-oxo-1-phenylpent-4-yn-2-yl)carbamate (209)

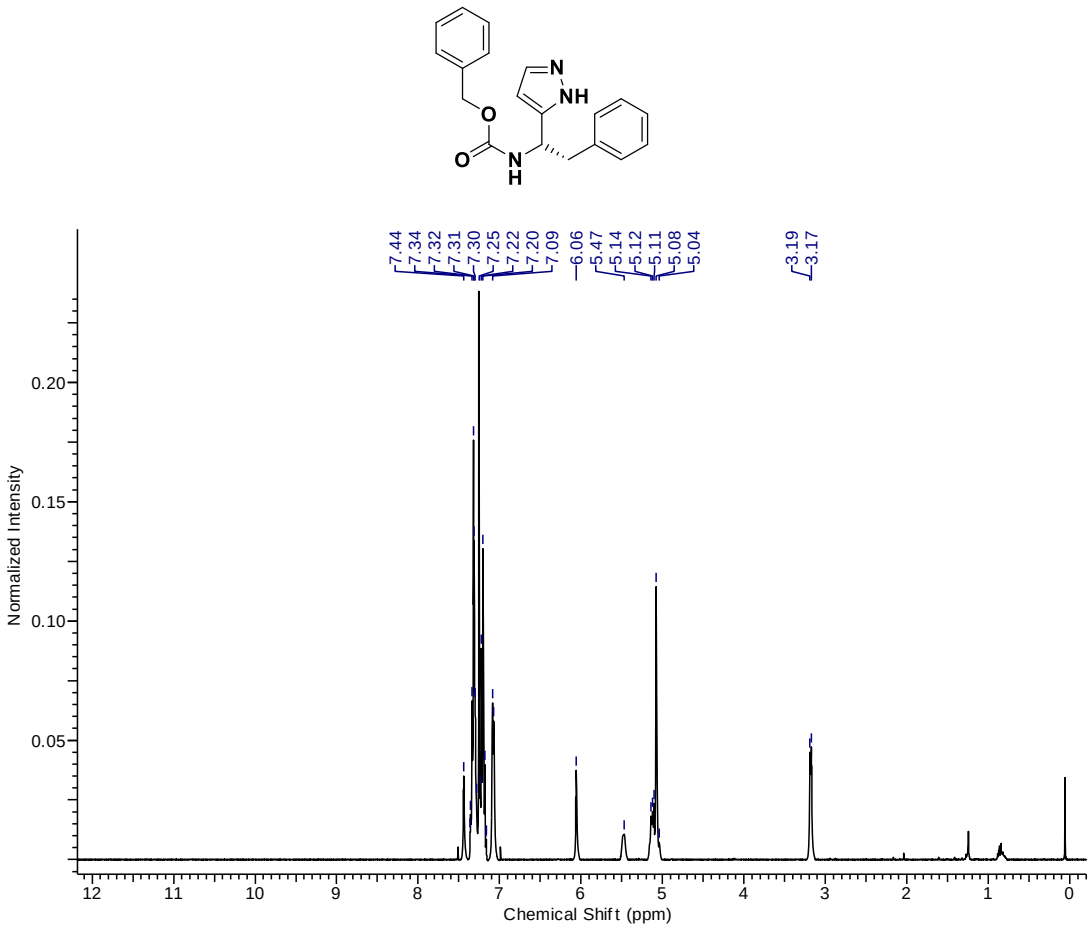


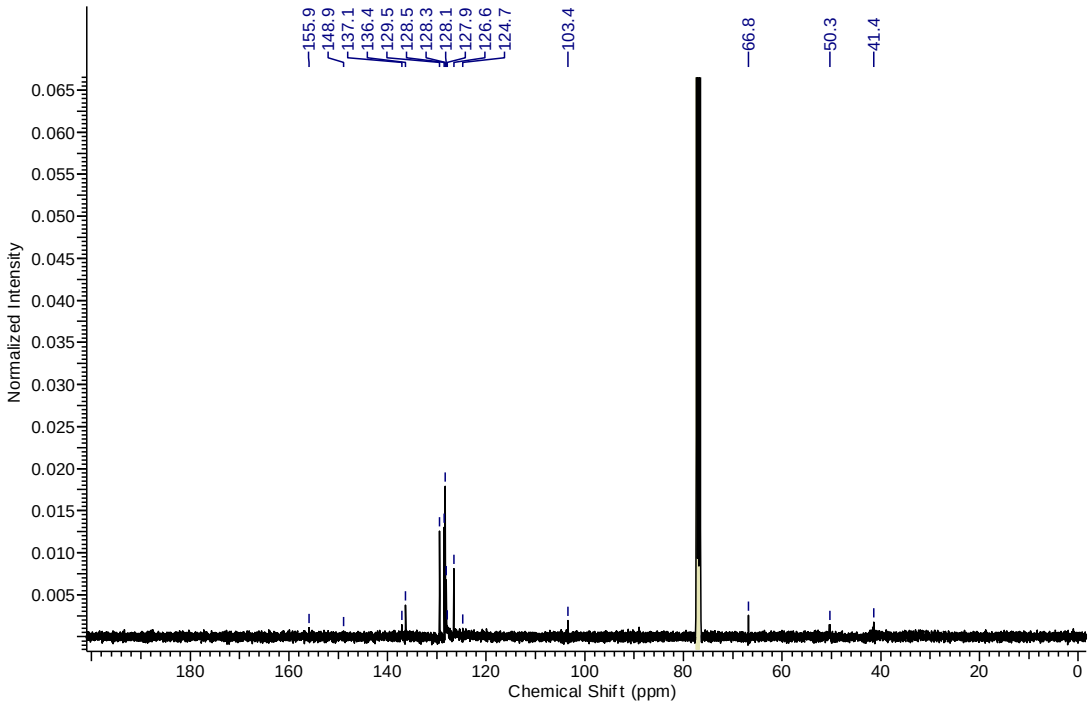


Benzyl (S)-(5-(diethylamino)-3-oxo-1-phenylpent-4-en-2-yl)carbamate (210)

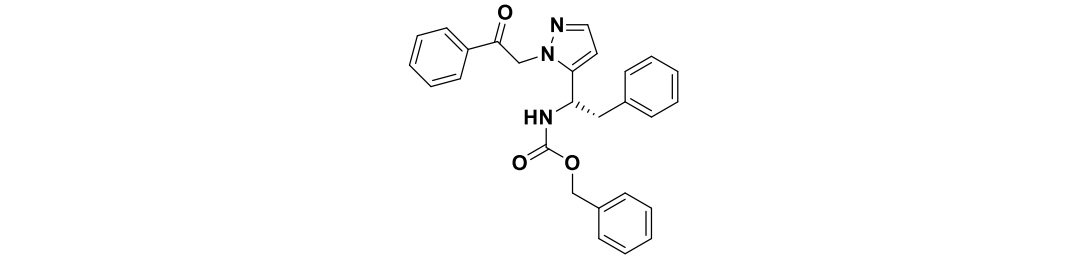


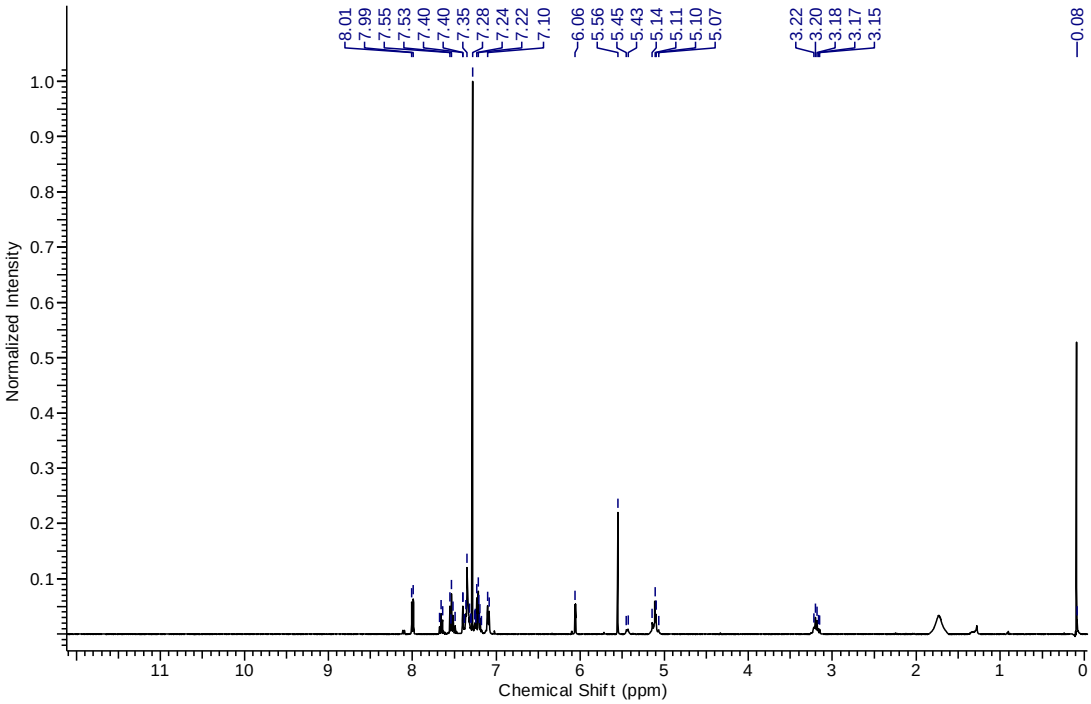
Benzyl (2-phenyl-1-(1H-pyrazol-5-yl)ethyl)carbamate (211)

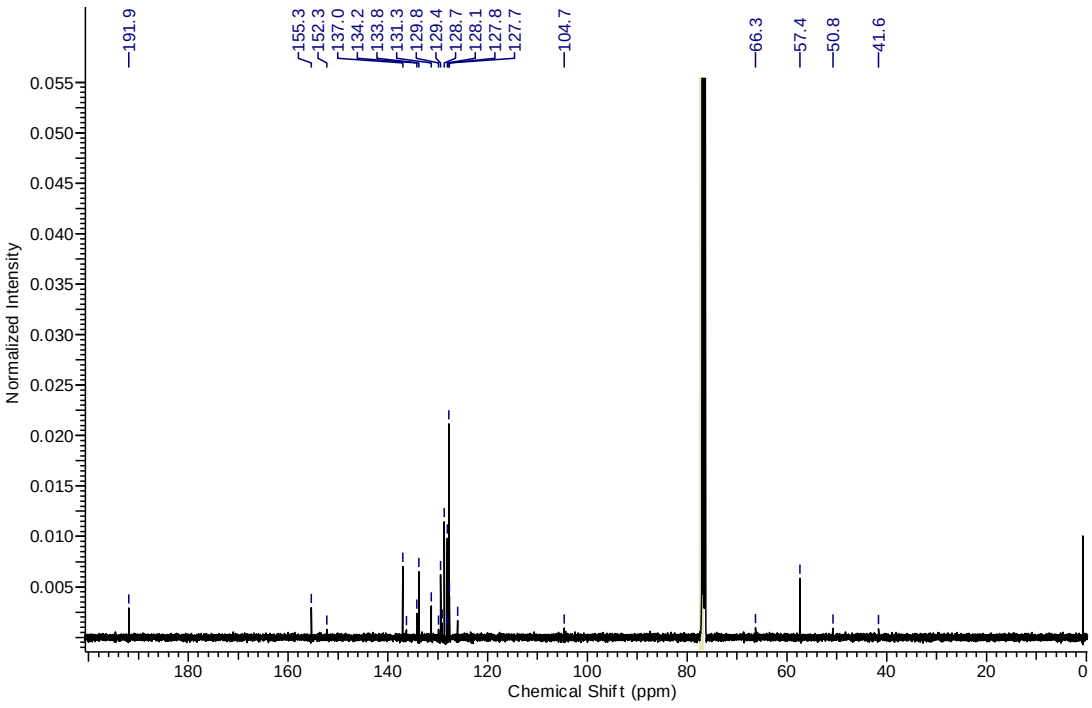




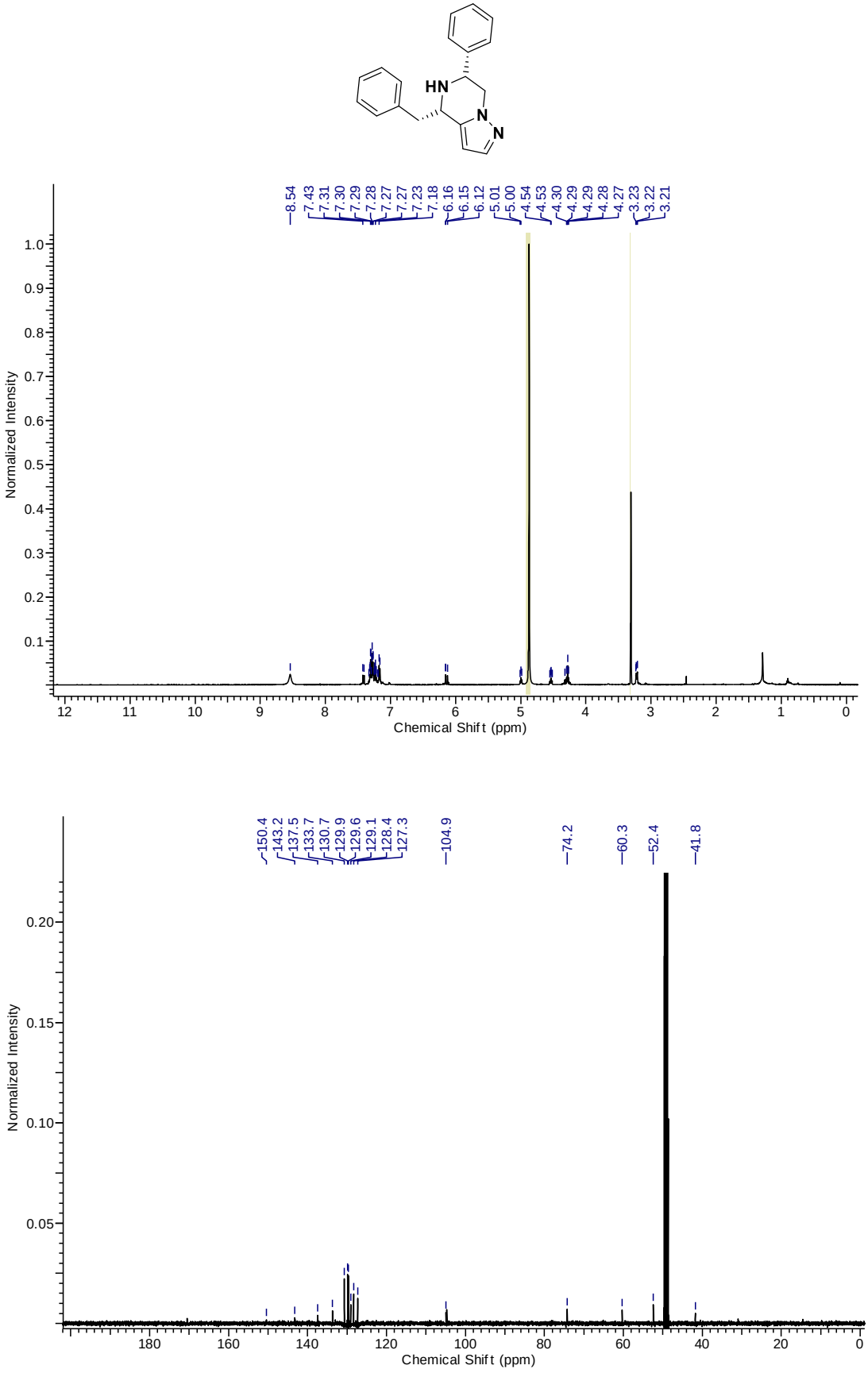
Benzyl (1-(1-(2-oxo-2-phenylethyl)-1H-pyrazol-5-yl)-2-phenylethyl)carbamate (212)



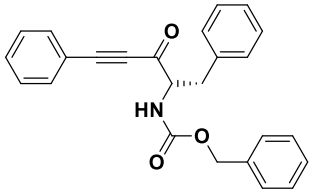


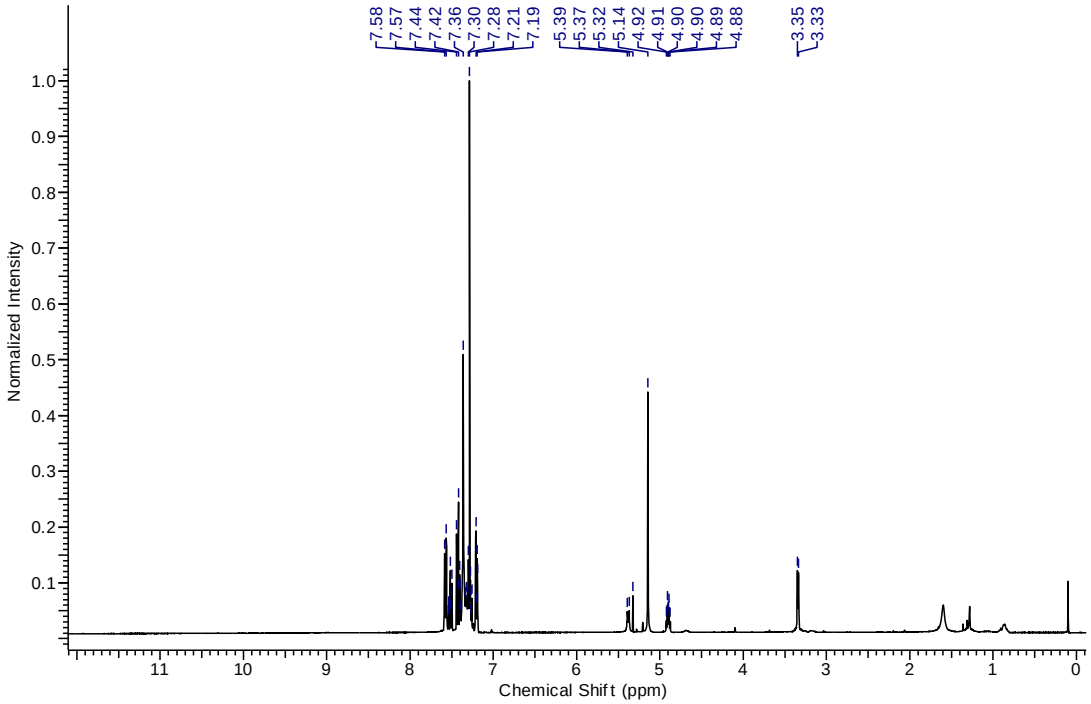


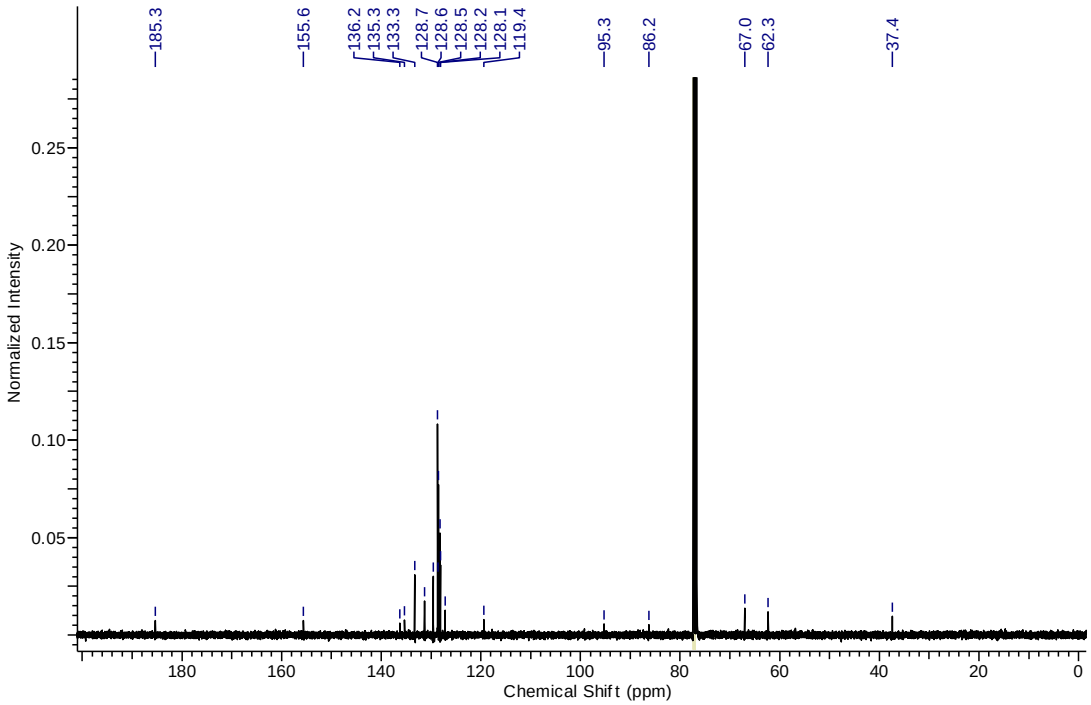
(4S,6R)-4-benzyl-6-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (213)



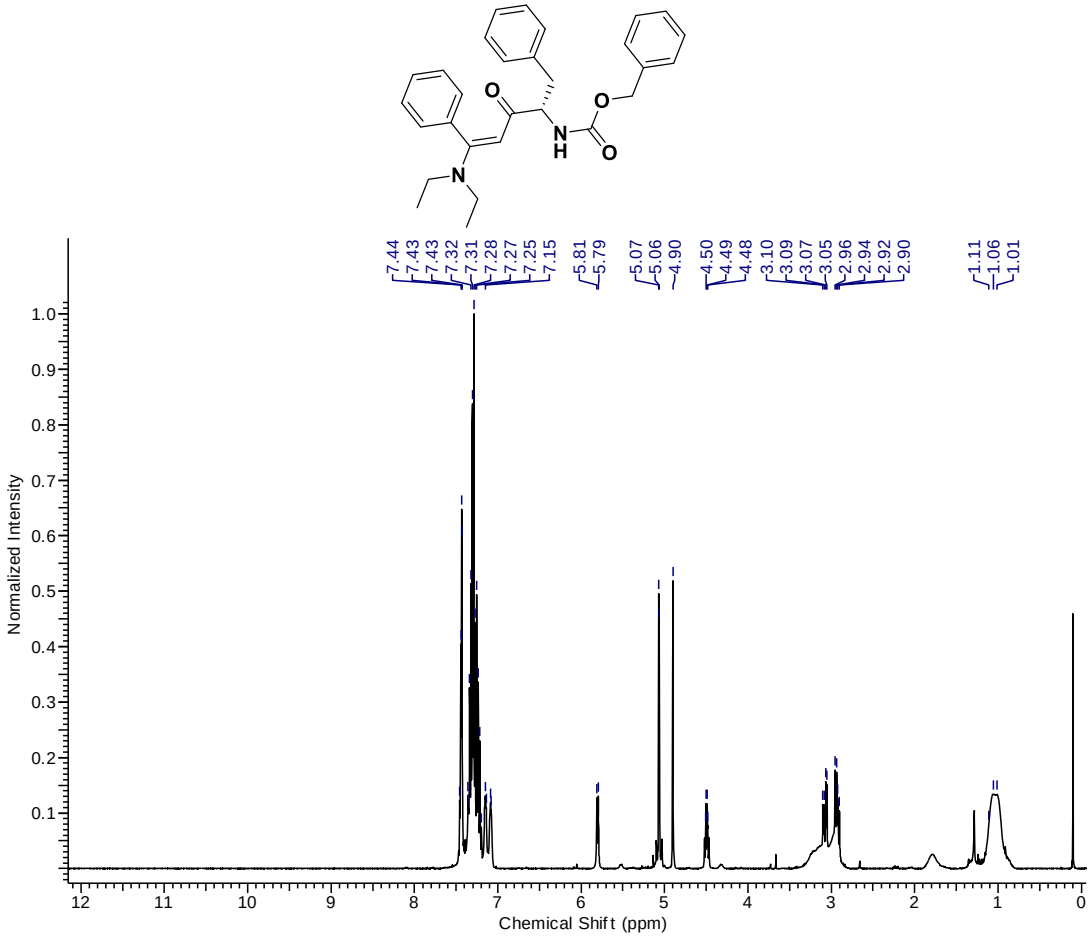
Benzyl (S)-(3-oxo-1,5-diphenylpent-4-yn-2-yl)carbamate (214)

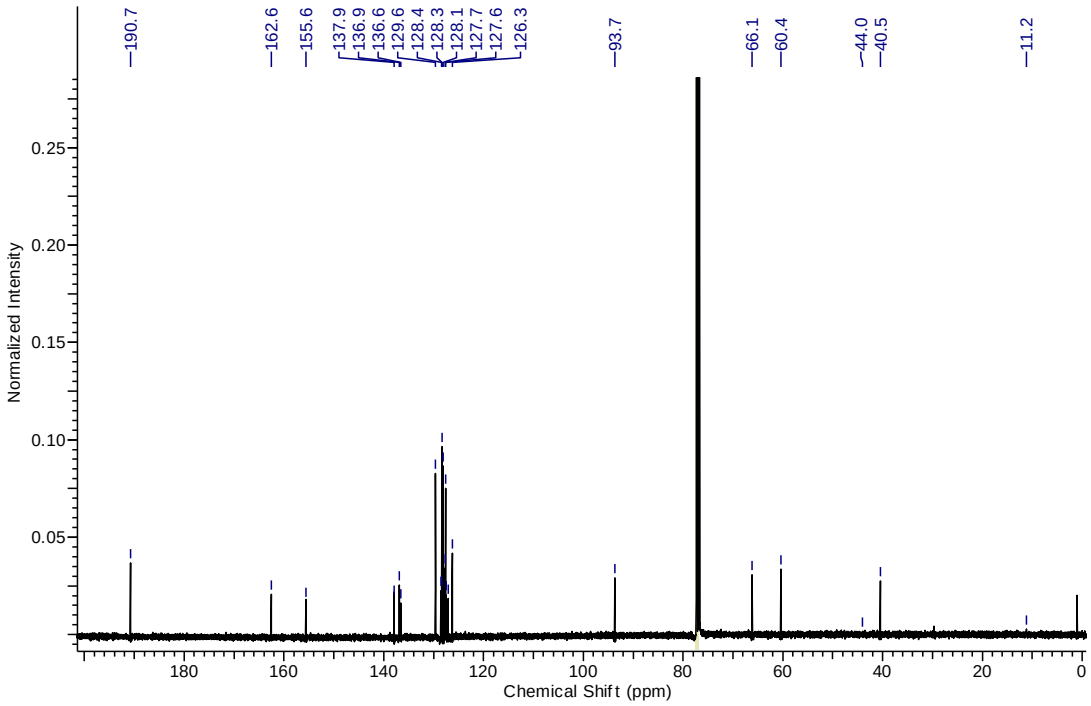




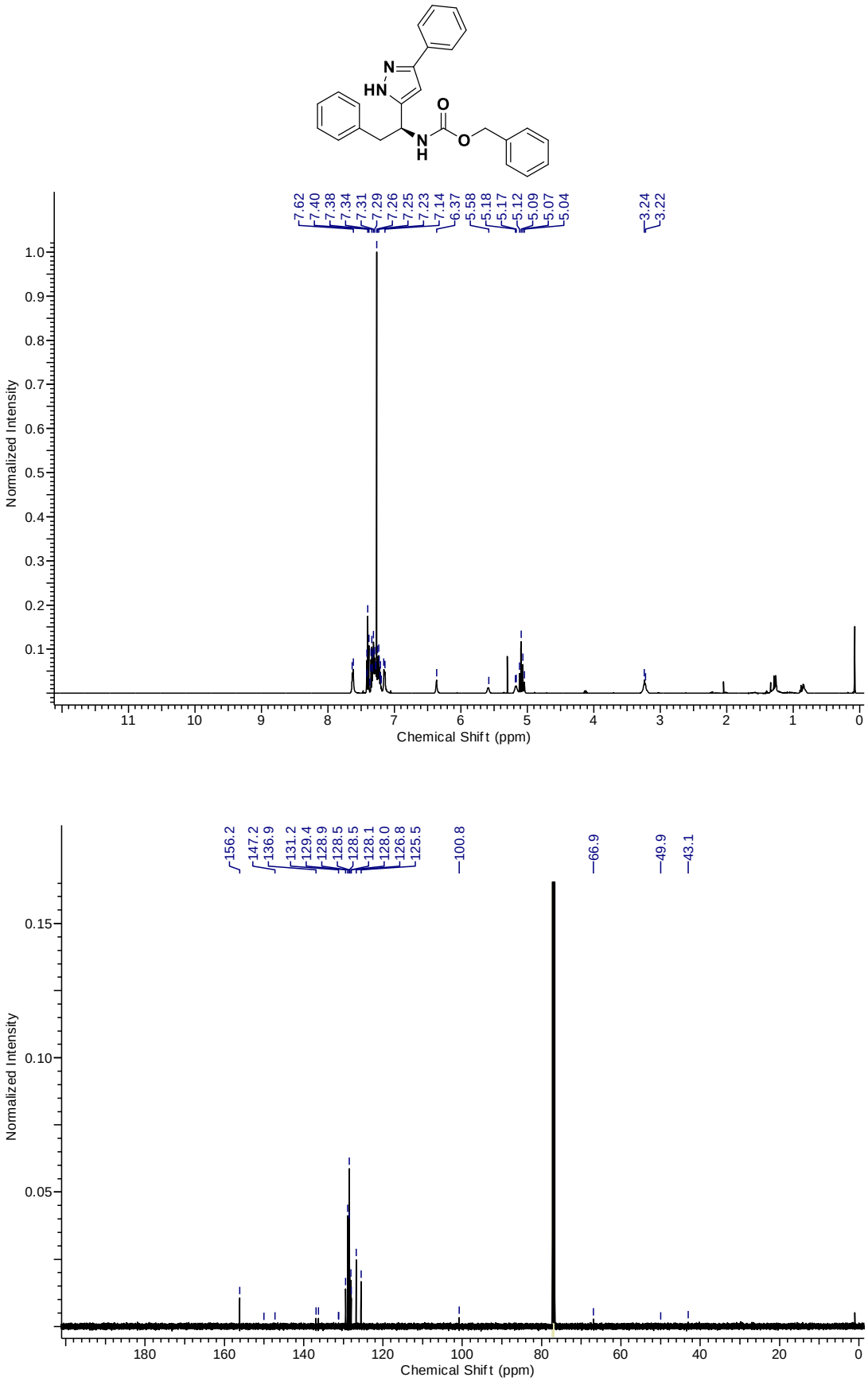


Benzyl (S,E)-(5-(diethylamino)-3-oxo-1,5-diphenylpent-4-en-2-yl)carbamate (215)

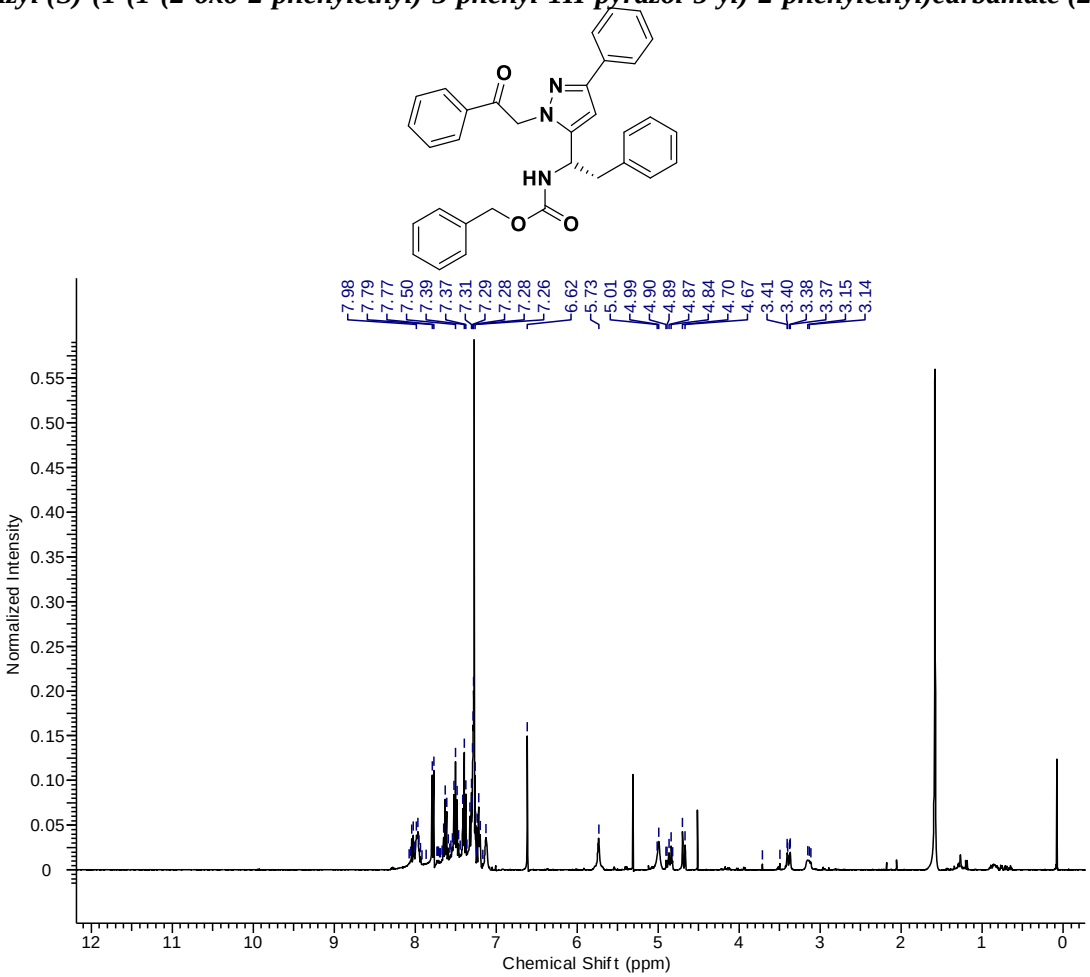


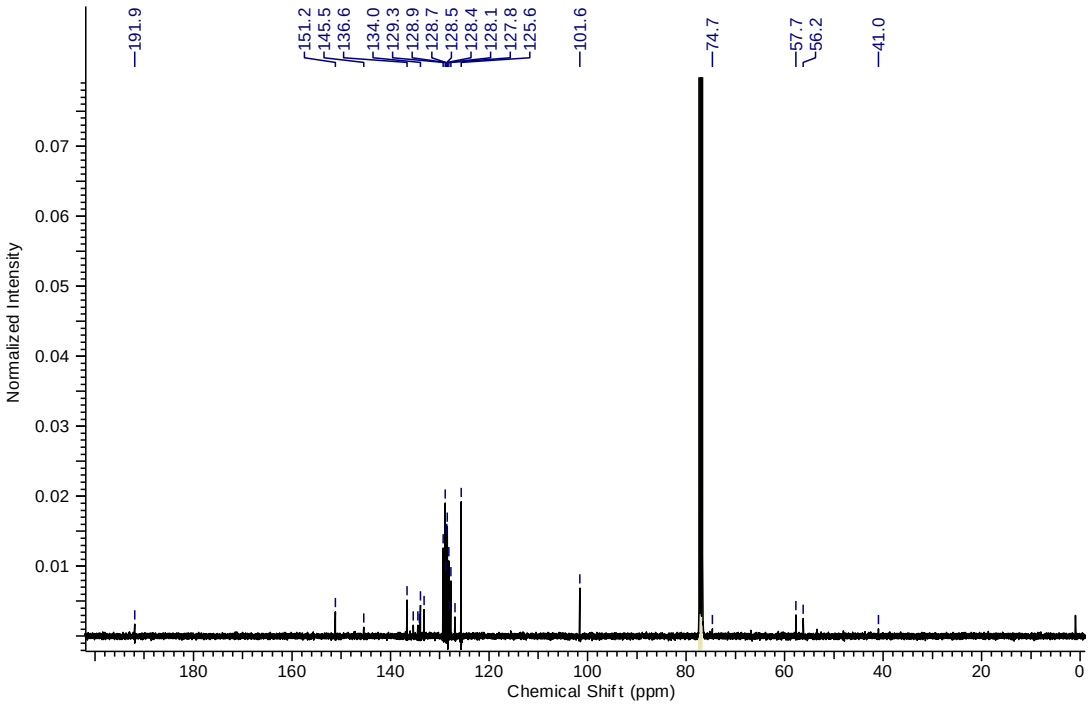


Benzyl (S)-(2-phenyl-1-(3-phenyl-1H-pyrazol-5-yl)ethyl)carbamate (216)

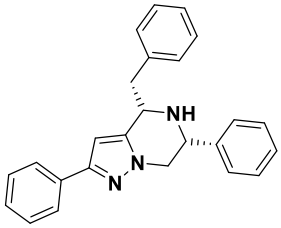


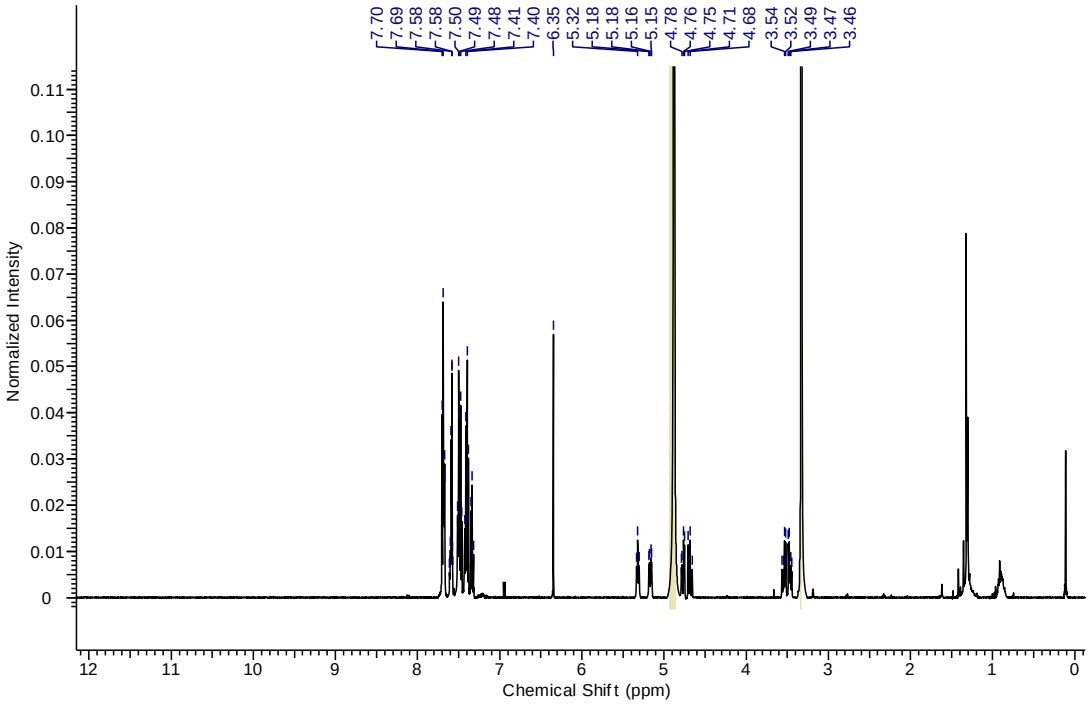
Benzyl (S)-(1-(1-(2-oxo-2-phenylethyl)-3-phenyl-1H-pyrazol-5-yl)-2-phenylethyl)carbamate (217)

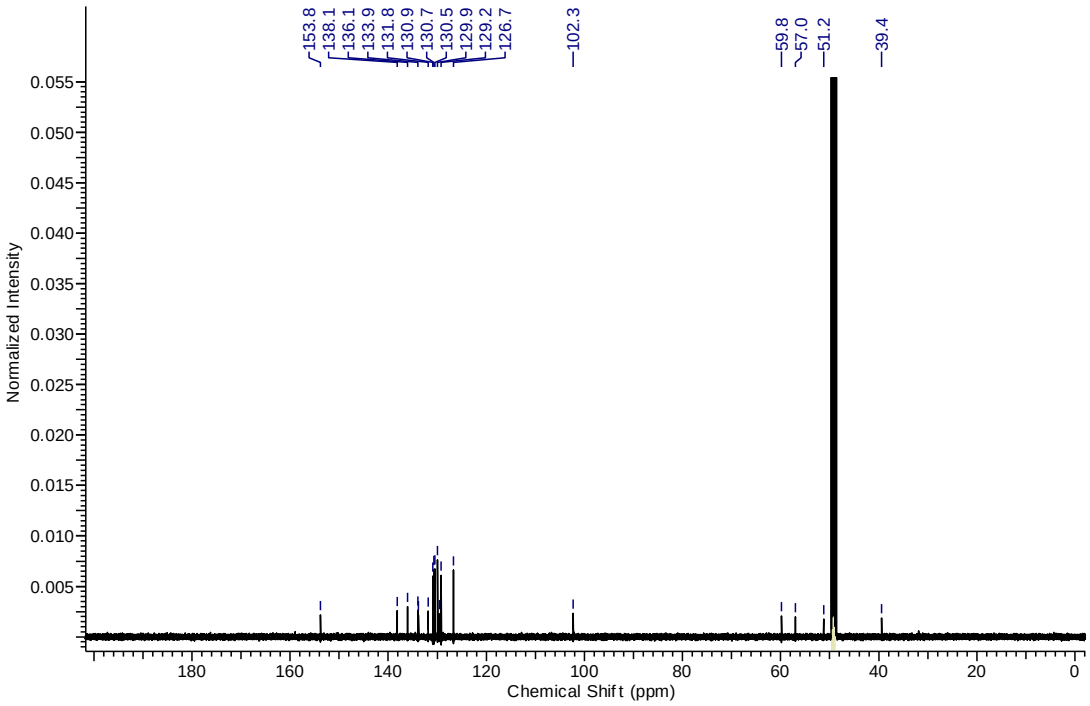




(4S,6R)-4-benzyl-2,6-diphenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (218)

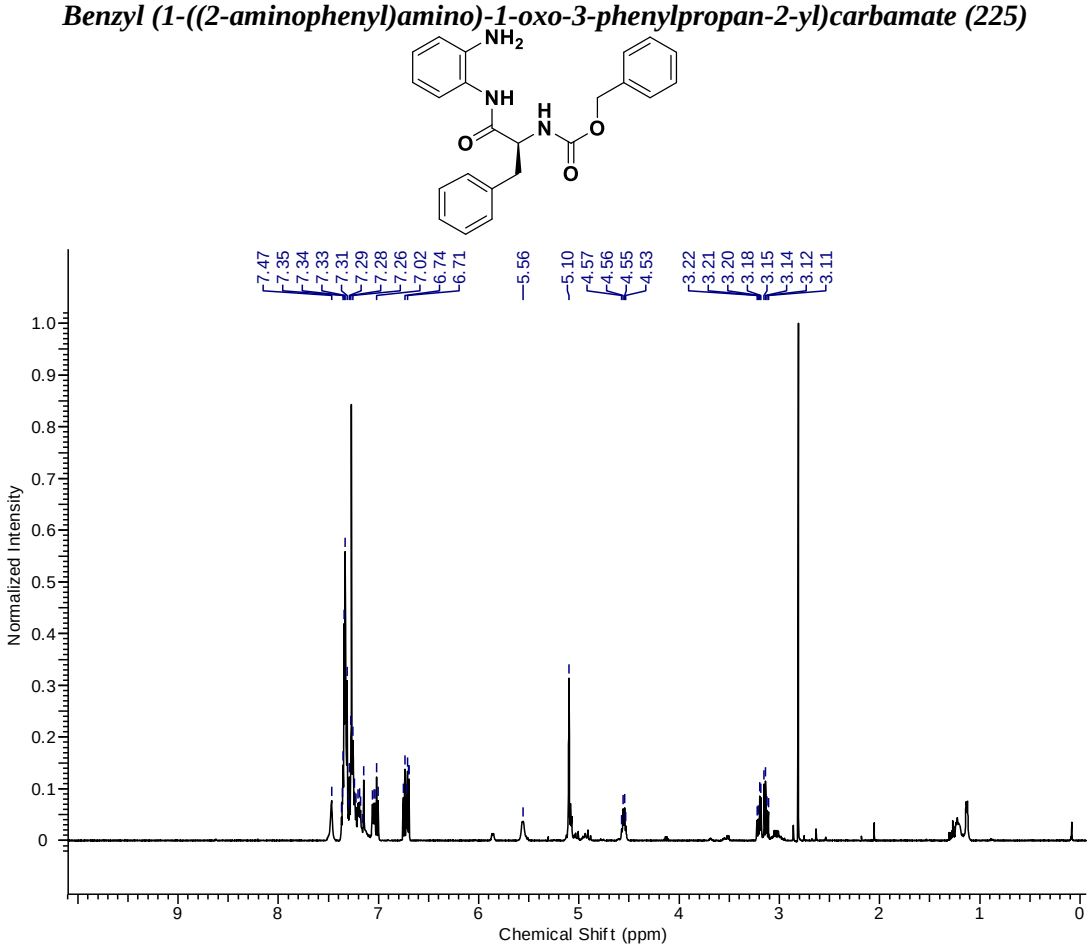


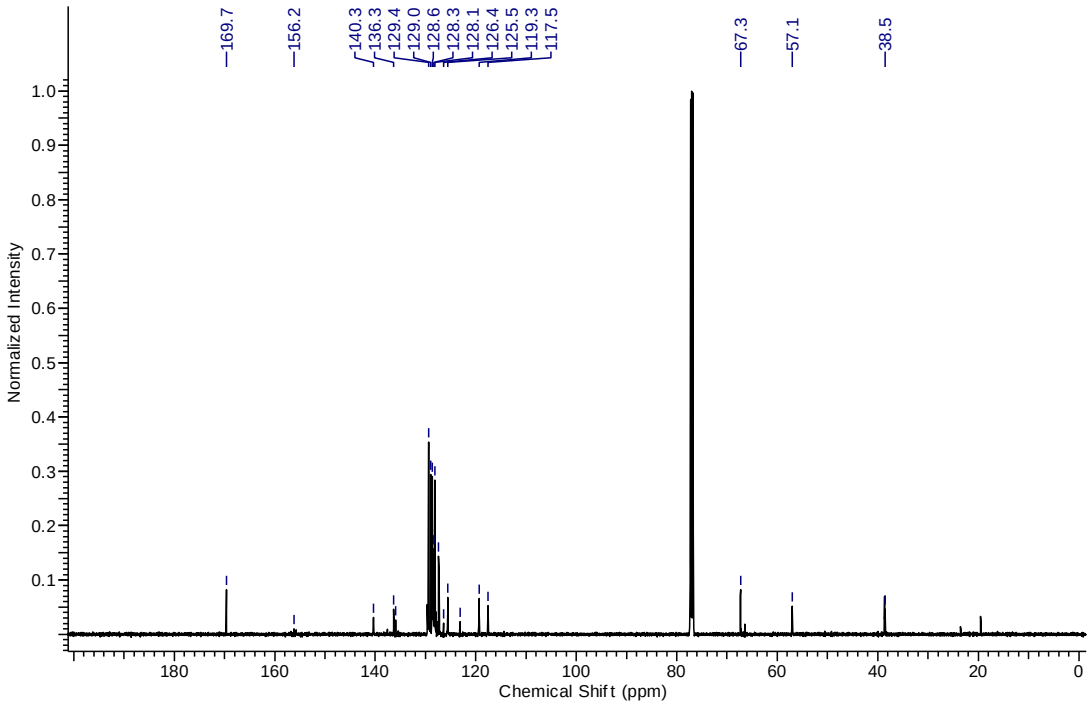




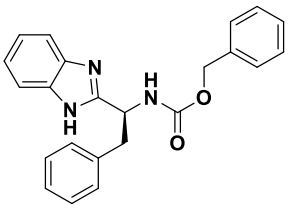
7.2.5. Efficient Synthesis of Benzimidazole-based Scaffolds

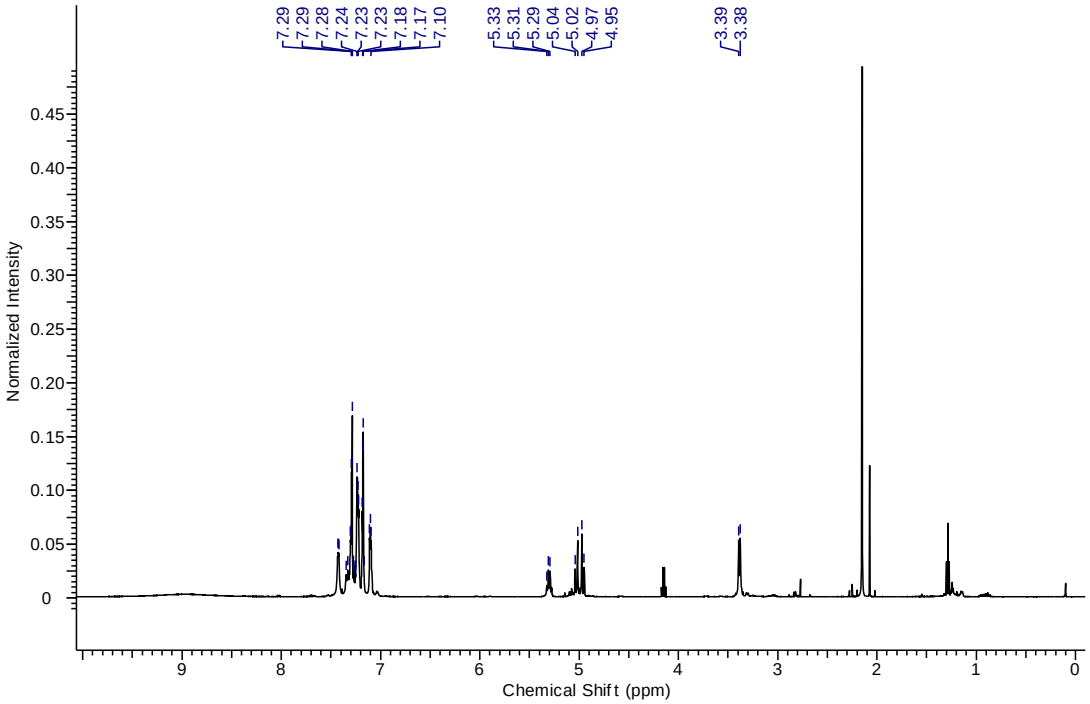
Benzyl (1-((2-aminophenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (225)

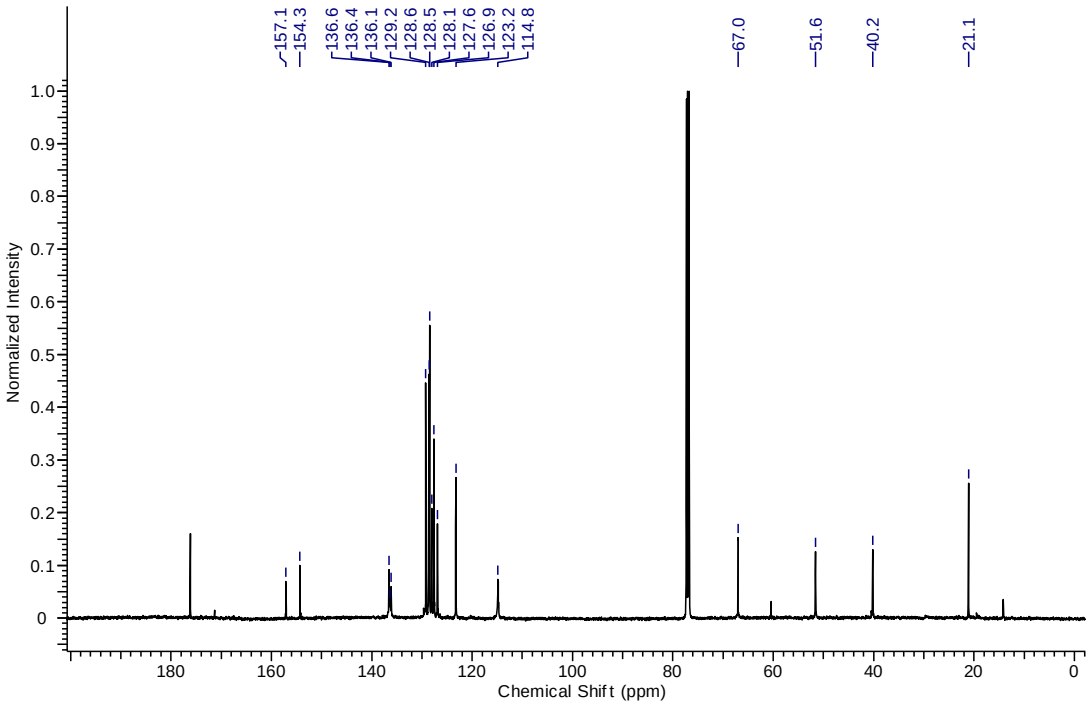




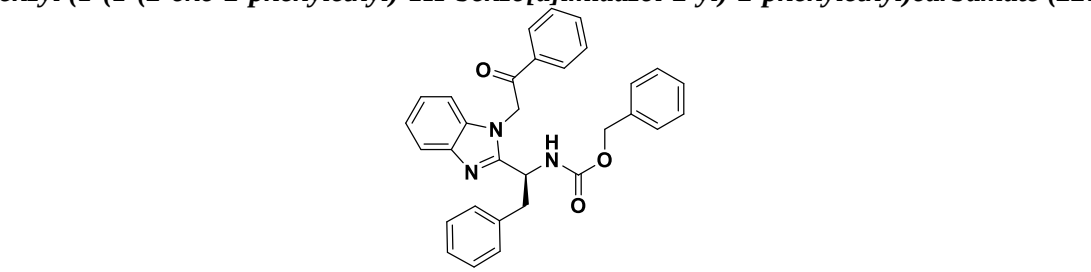
Benzyl (1-(1H-benzo[d]imidazol-2-yl)-2-phenylethyl)carbamate (226)

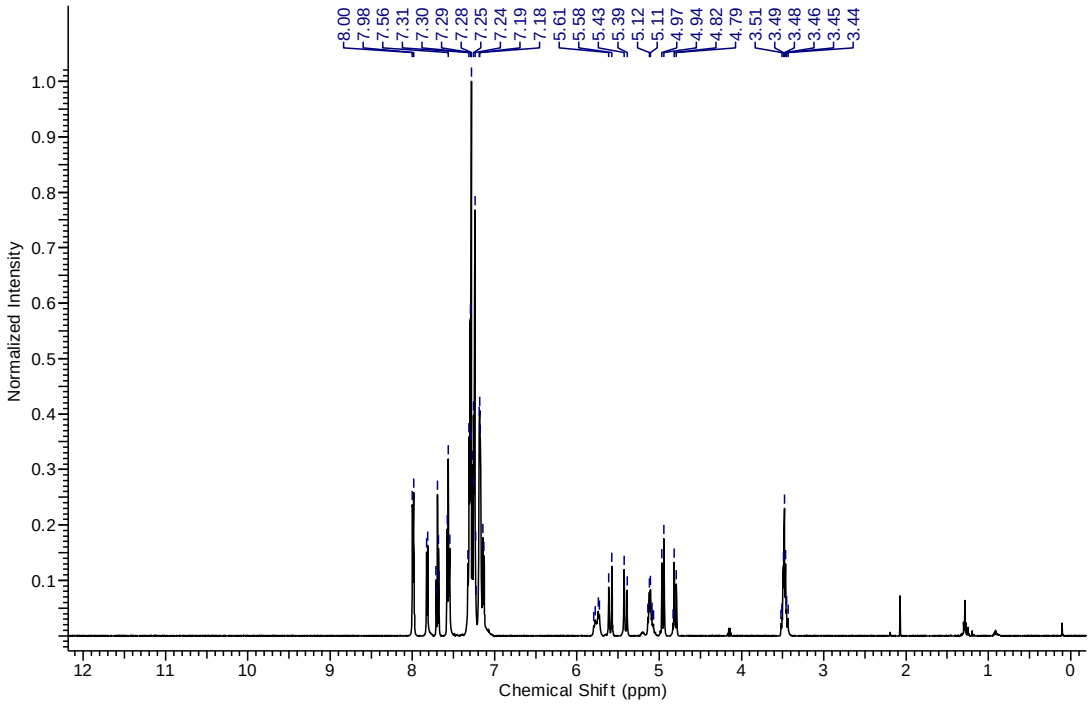


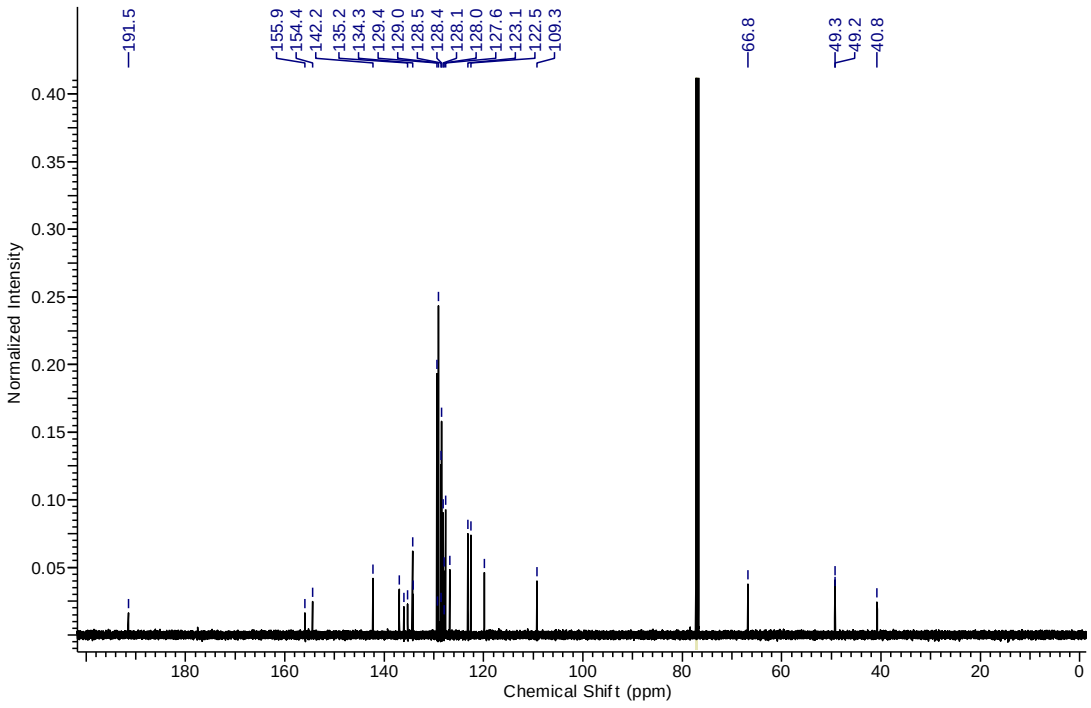




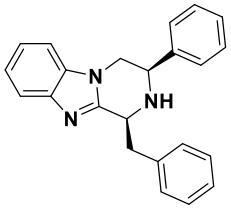
Benzyl (1-(1-(2-oxo-2-phenylethyl)-1H-benzo[d]imidazol-2-yl)-2-phenylethyl)carbamate (227)

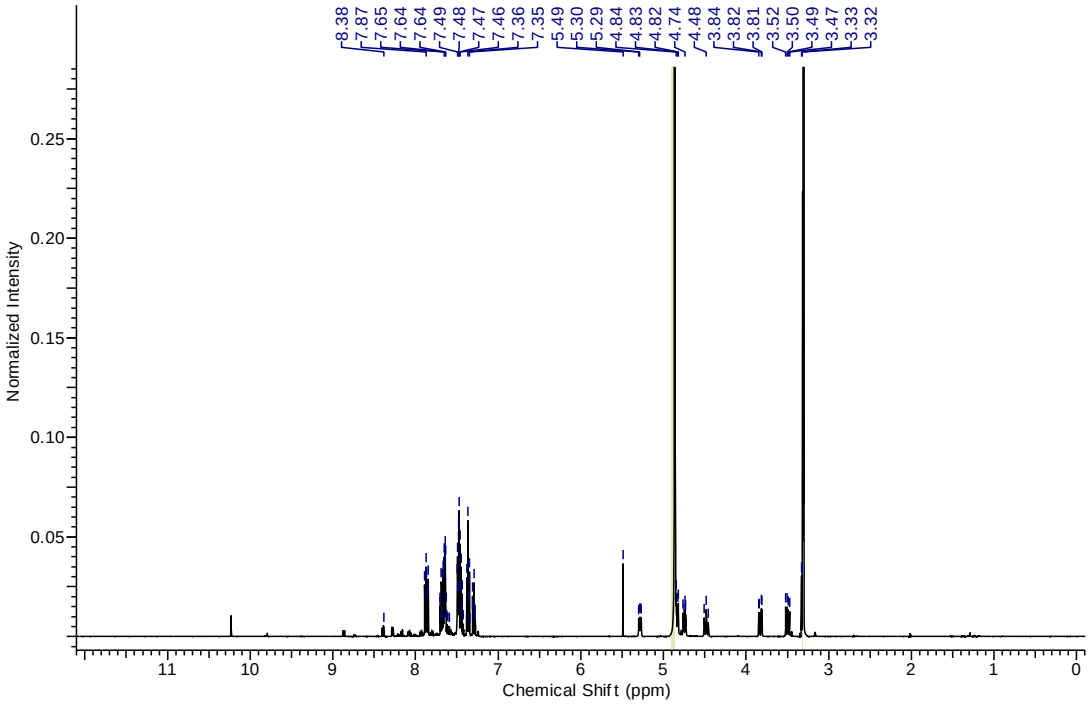


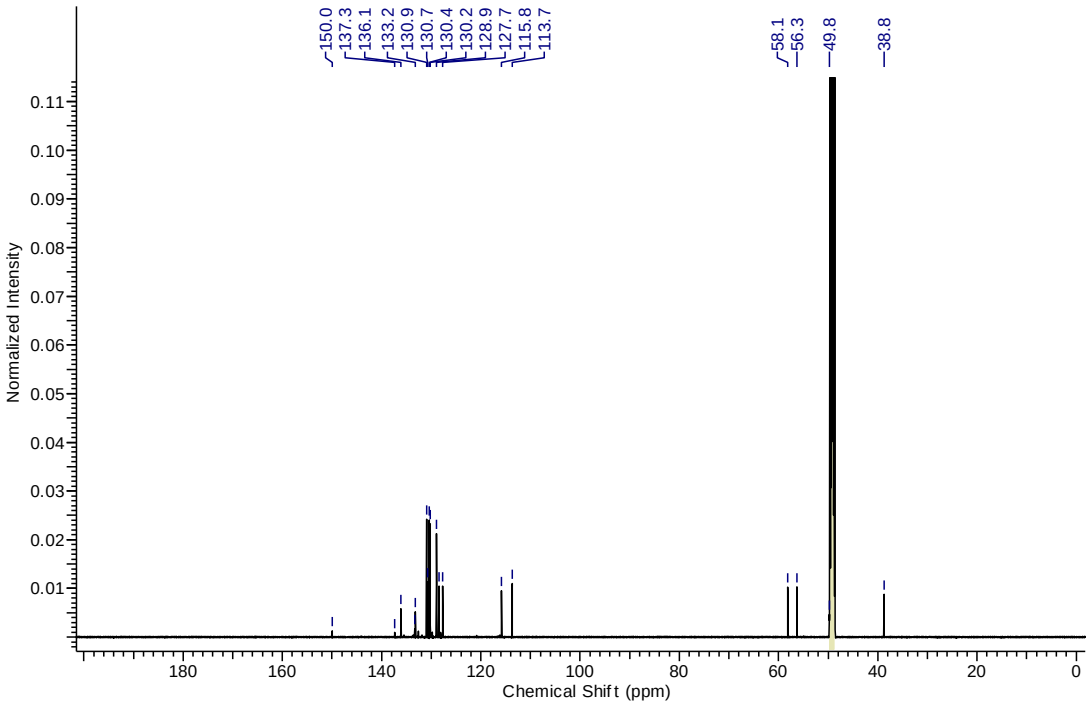




(1S,3R)-1-benzyl-3-phenyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazine (228)

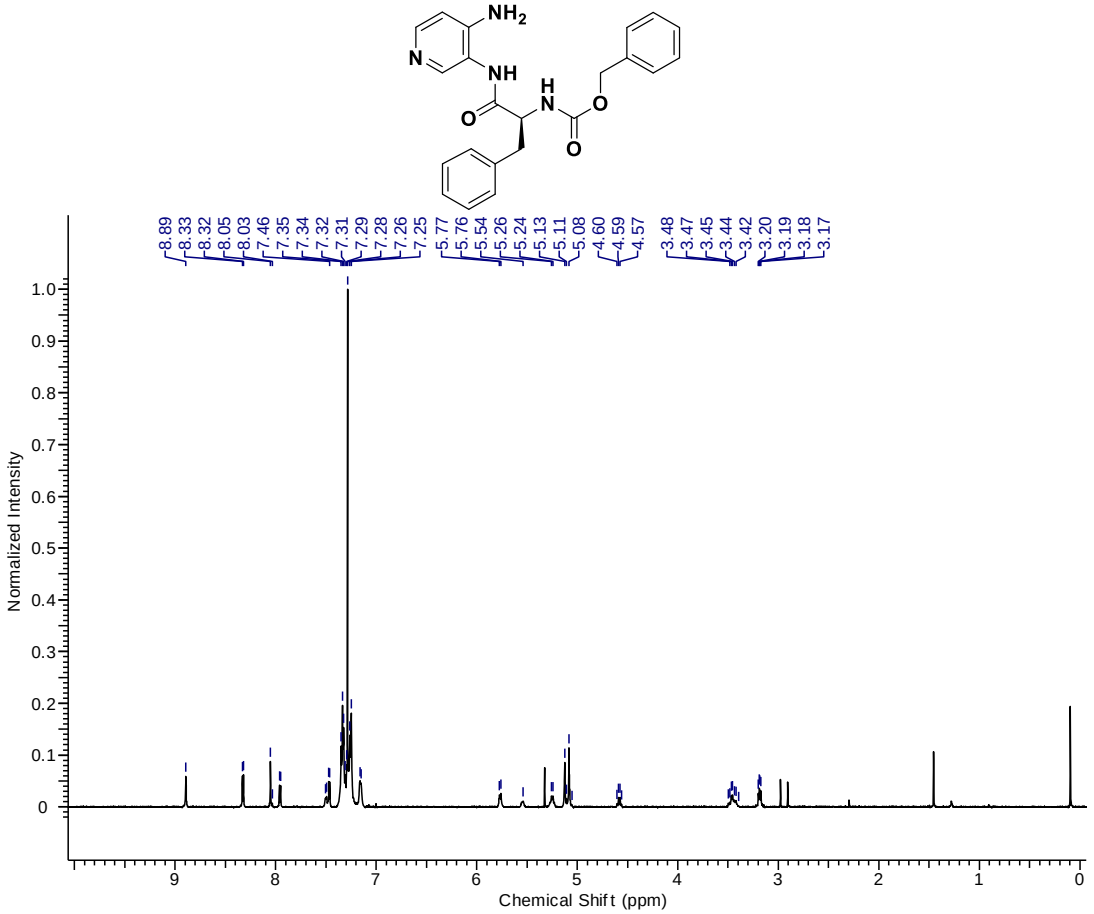


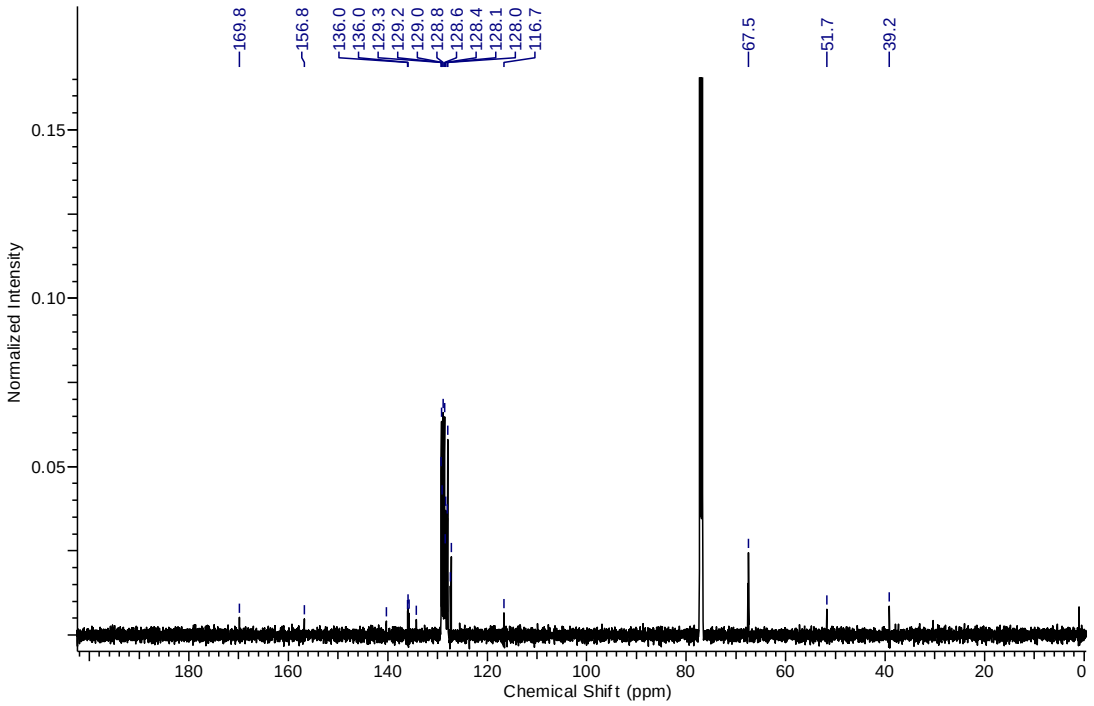




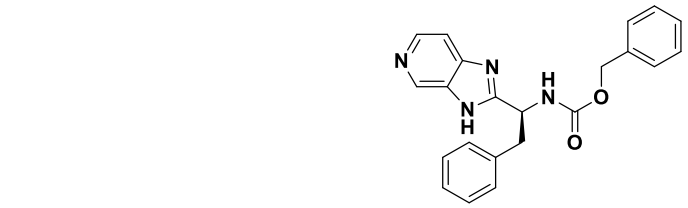
7.2.6. Efficient Synthesis of Imidazopyridine-based Scaffolds

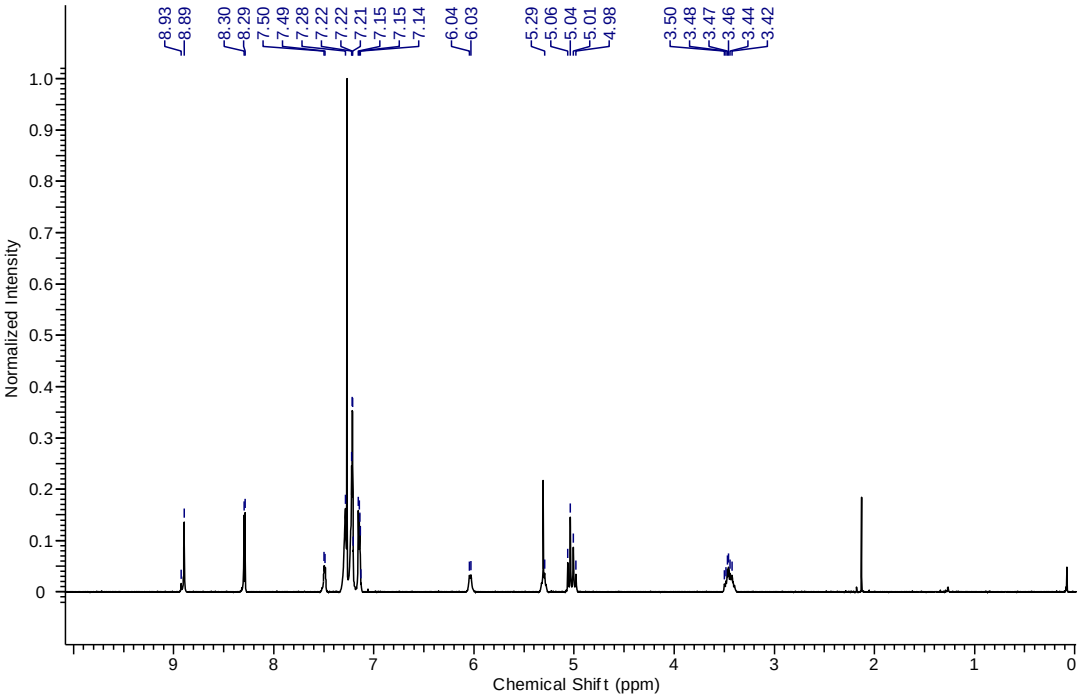
Benzyl (1-((4-aminopyridin-3-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (235)

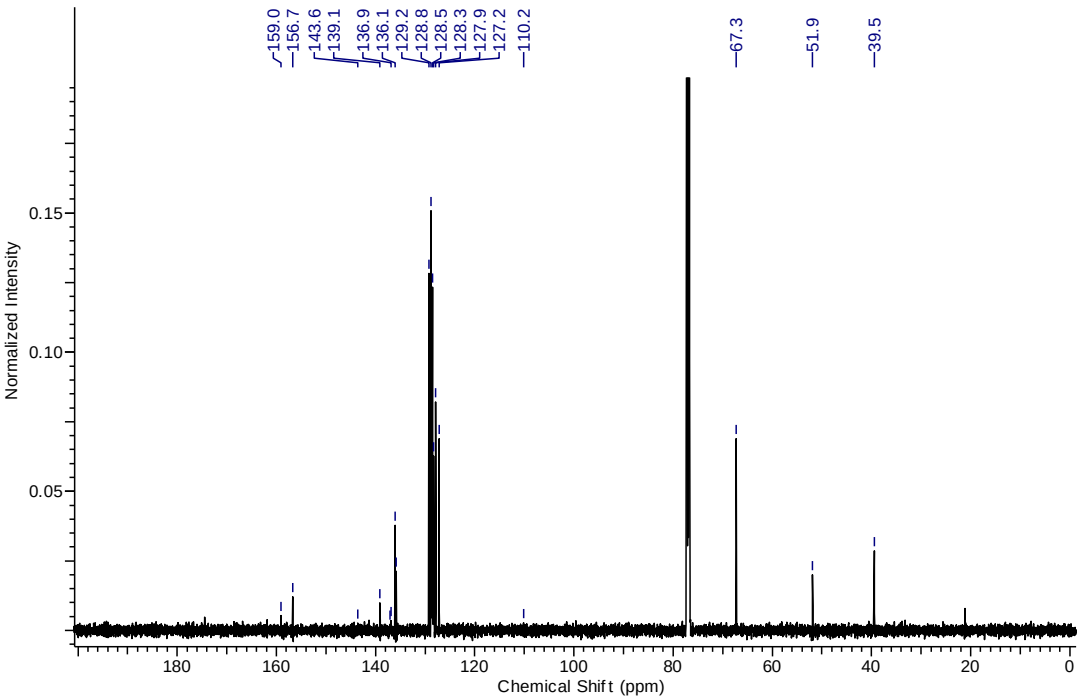




Benzyl (1-(3H-imidazo[4,5-c]pyridin-2-yl)-2-phenylethyl)carbamate (236)

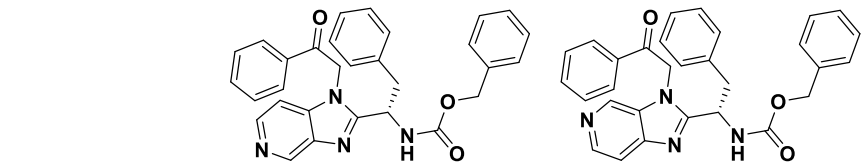


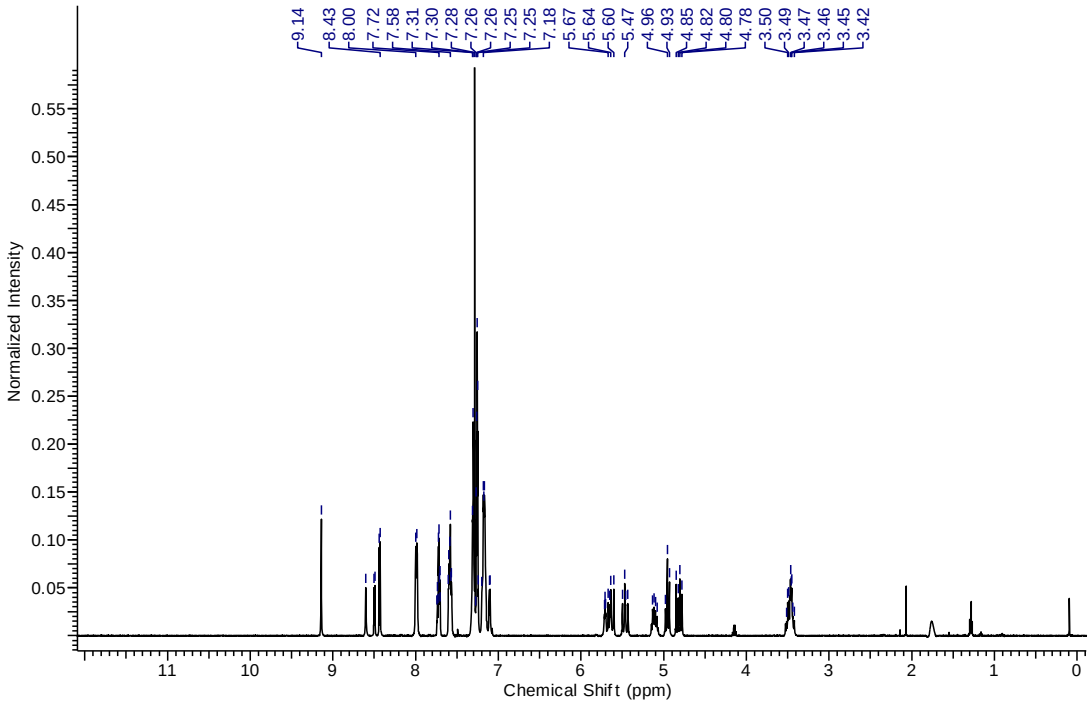


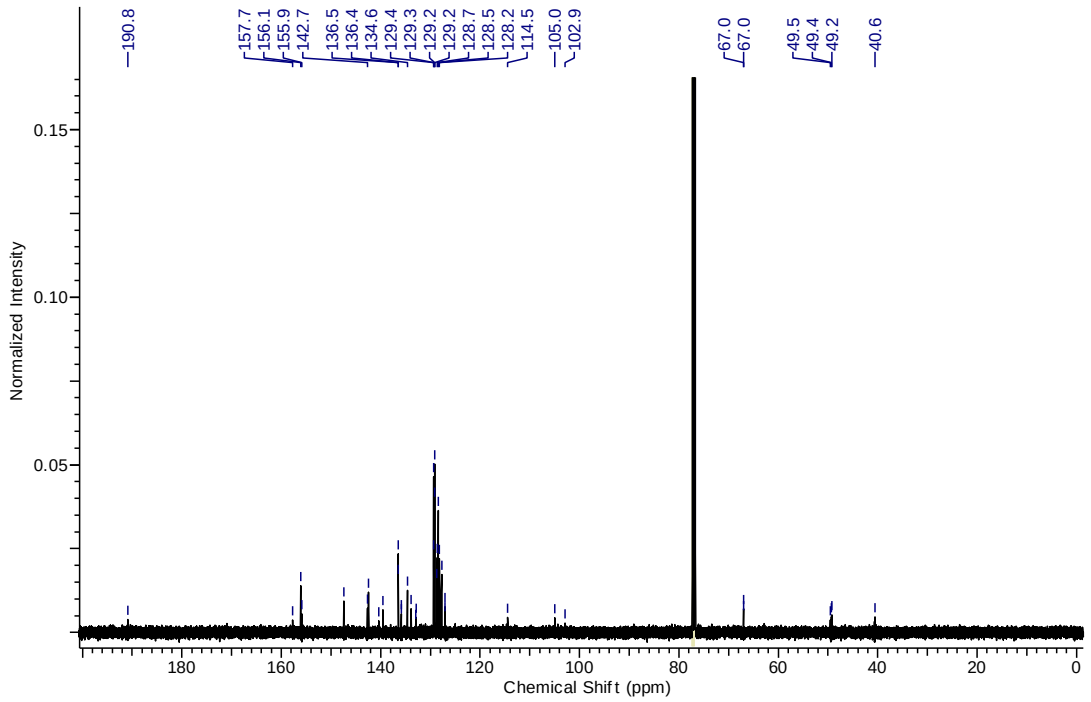


Benzyl (1-(1-(2-oxo-2-phenylethyl)-1H-imidazo[4,5-c]pyridin-2-yl)-2-phenylethyl)carbamate (237),

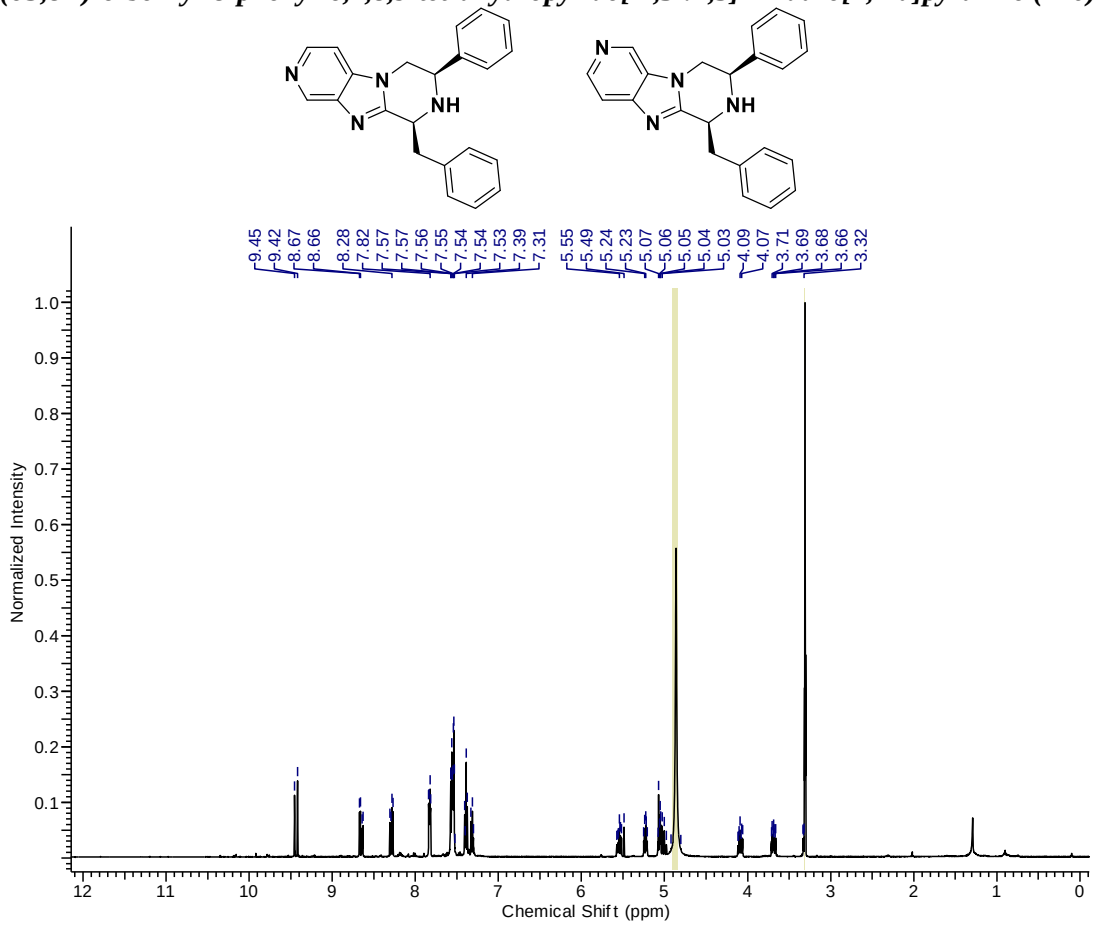
Benzyl (1-(3-(2-oxo-2-phenylethyl)-3H-imidazo[4,5-c]pyridin-2-yl)-2-phenylethyl)carbamate (238)

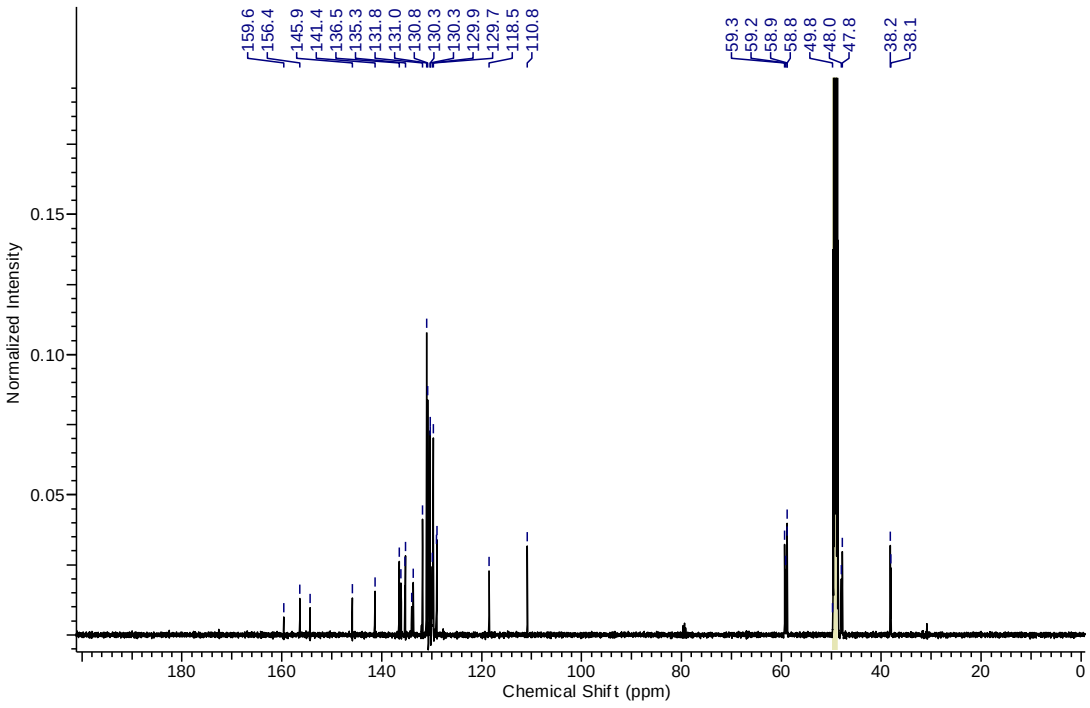






(7R,9S)-9-benzyl-7-phenyl-6,7,8,9-tetrahydropyrido[3',4':4,5]-imidazo[1,2-a]pyrazine (239) and (6S,8R)-6-benzyl-8-phenyl-6,7,8,9-tetrahydropyrido[4',3':4,5] imidazo[1,2-a]pyrazine (240)

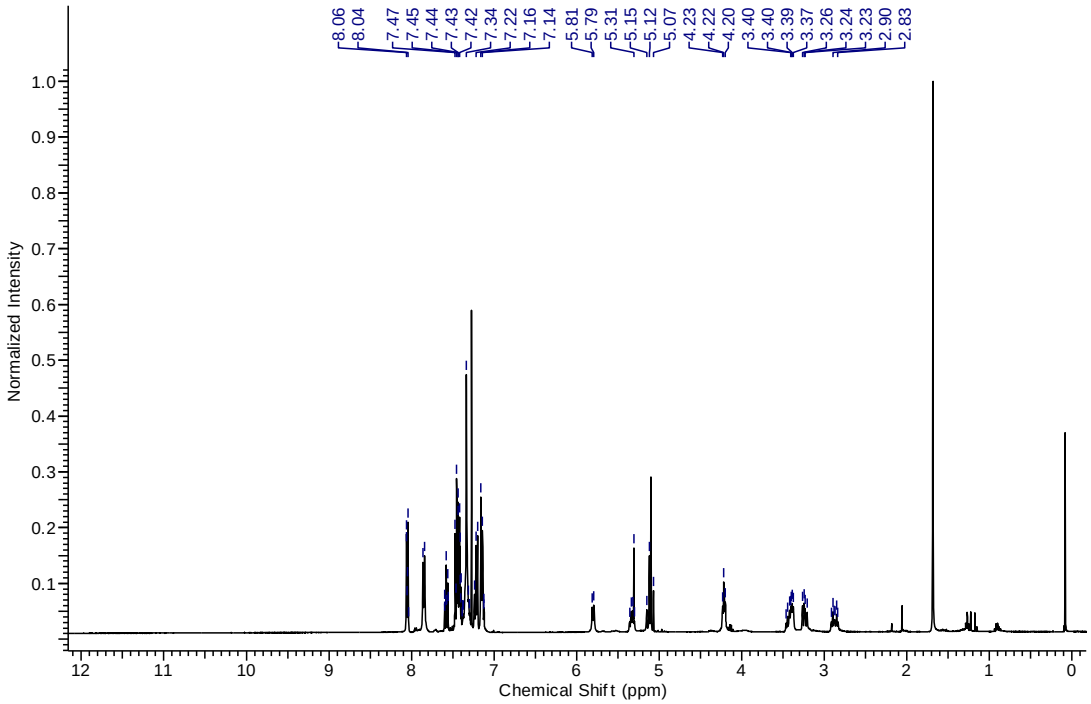


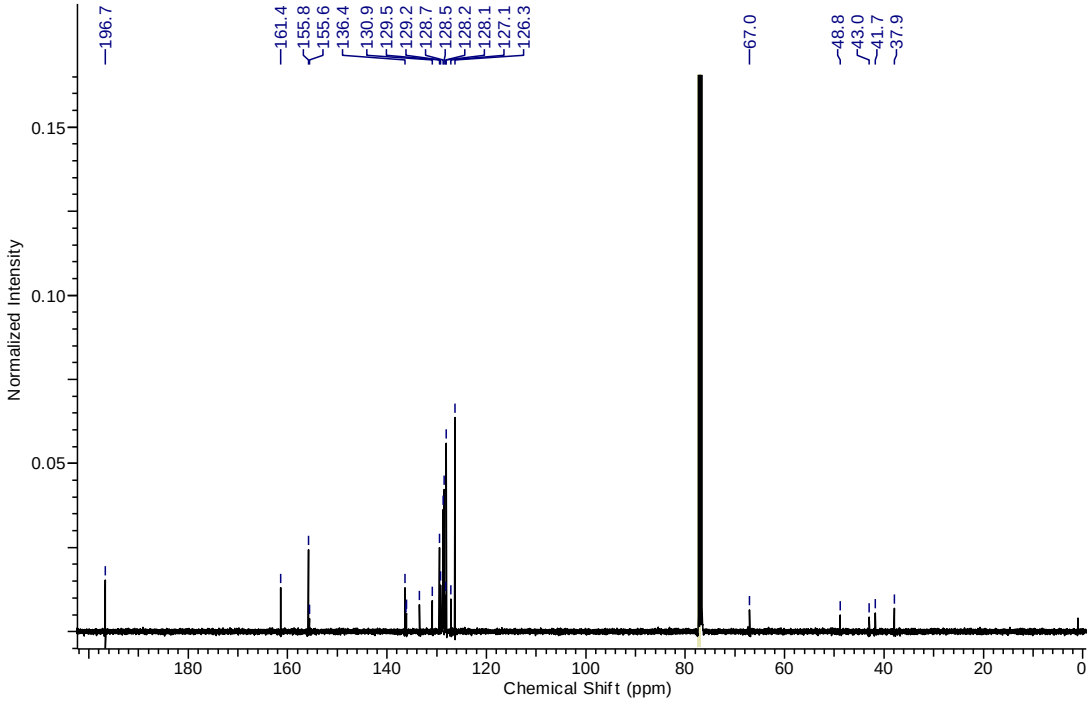


7.2.7. Efficient Synthesis of Larger Scaffolds.

Benzyl (S)-(1-(1-(3-oxo-3-phenylpropyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-phenylethyl)carbamate

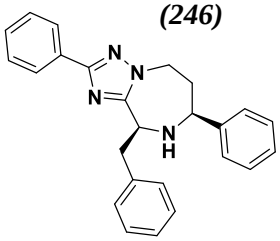
(245)

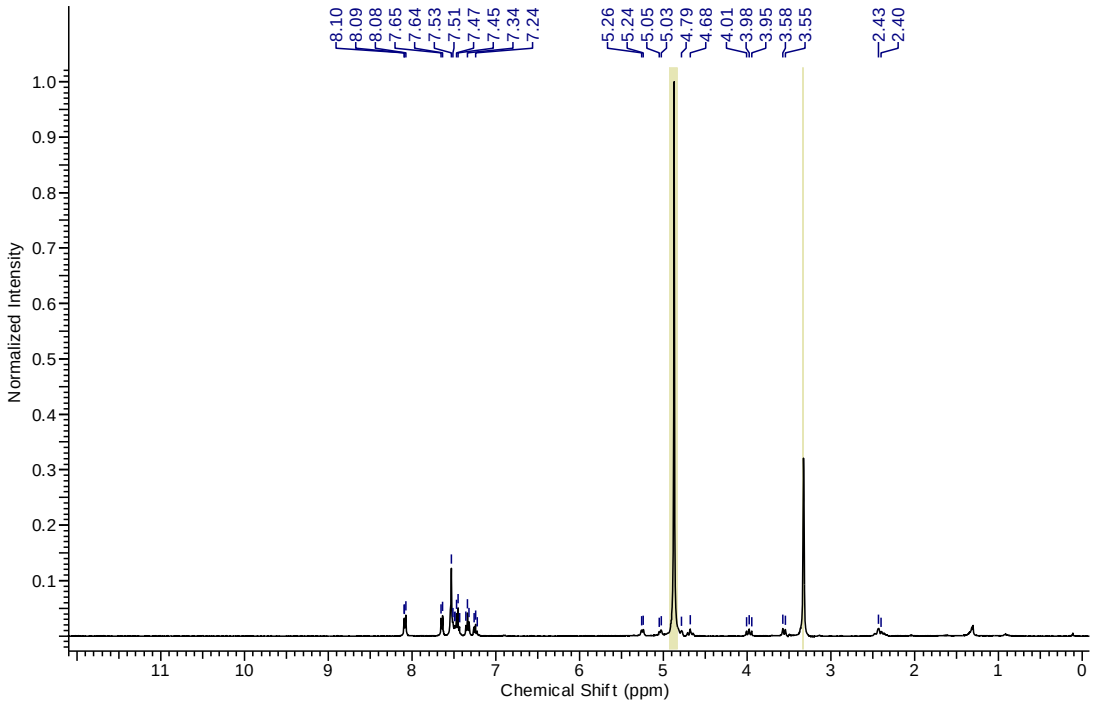


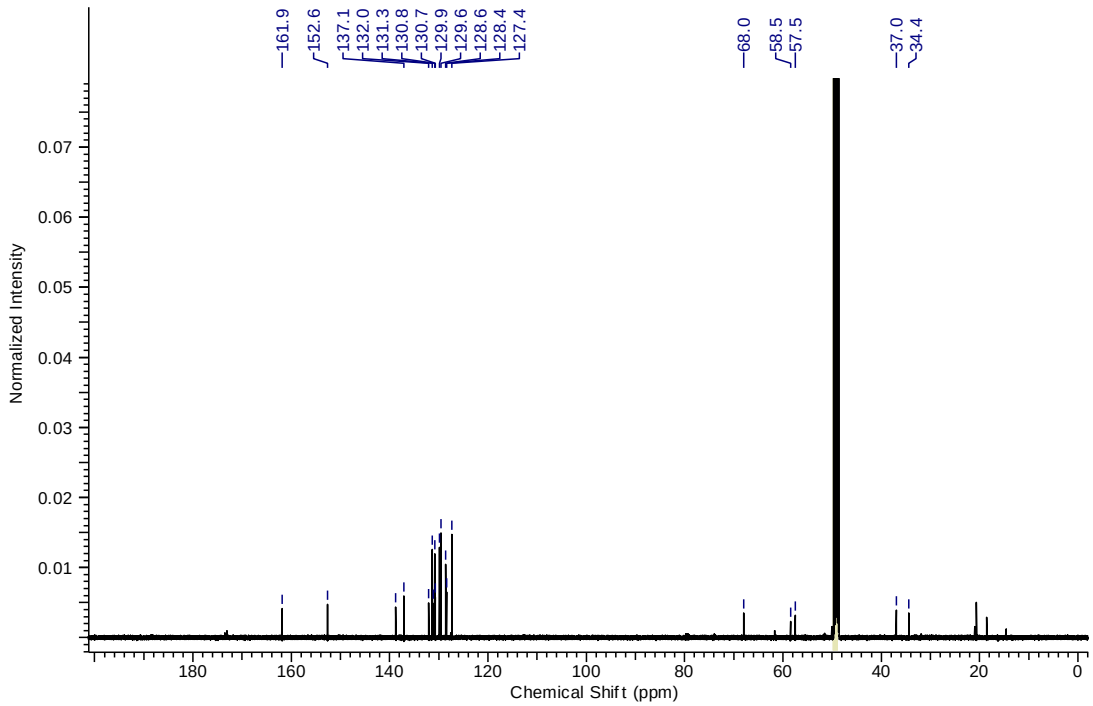


(7S,9S)-9-benzyl-2,7-diphenyl-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[1,5-a][1,4]diazepine

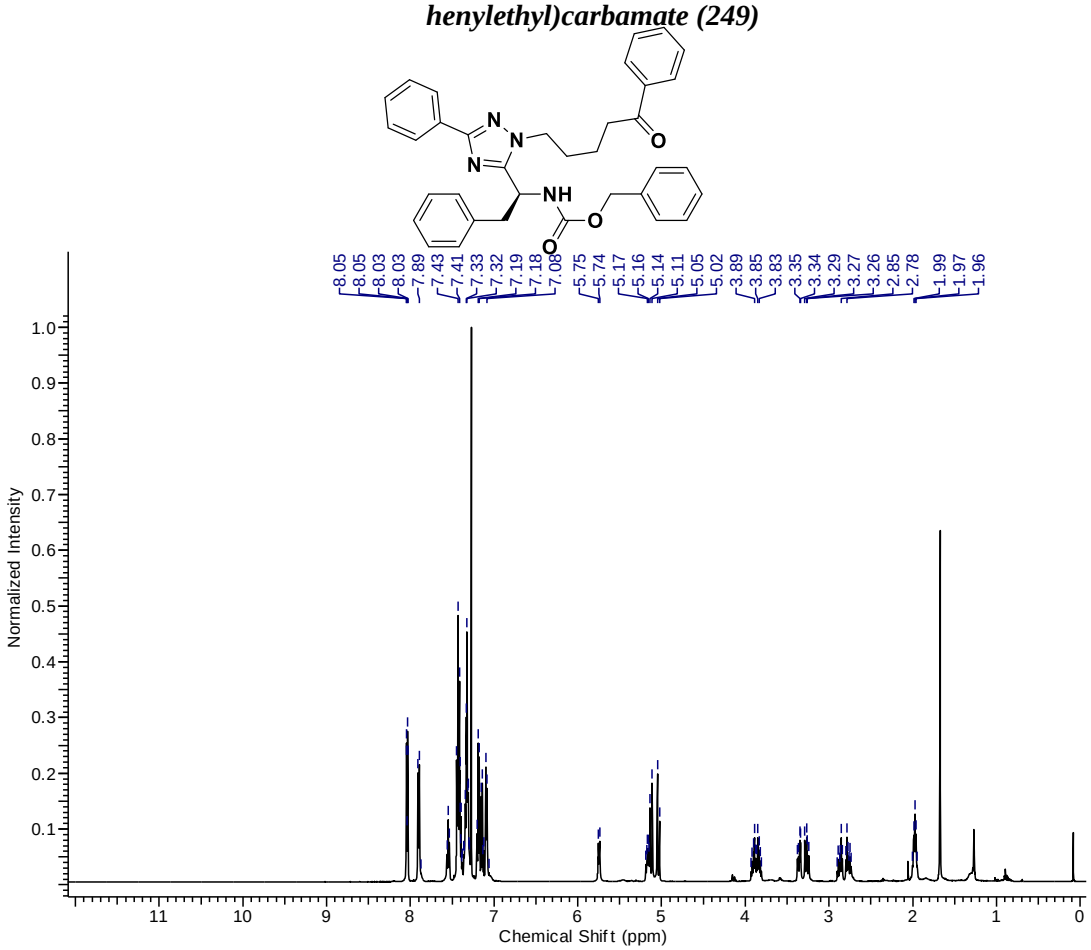
(246)

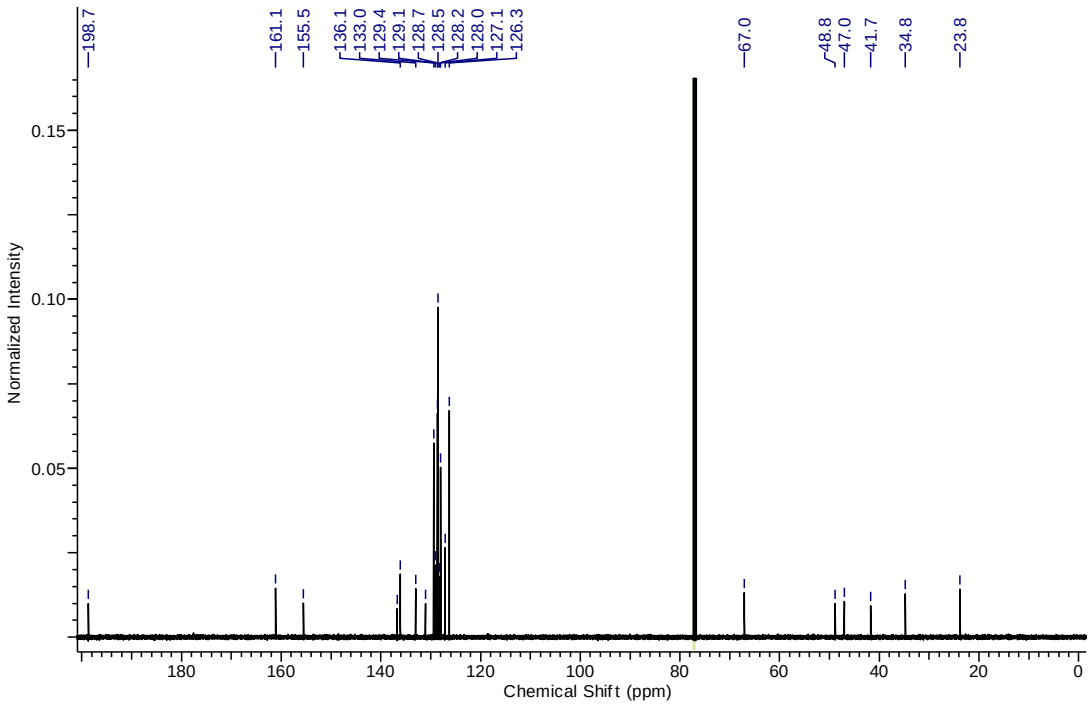






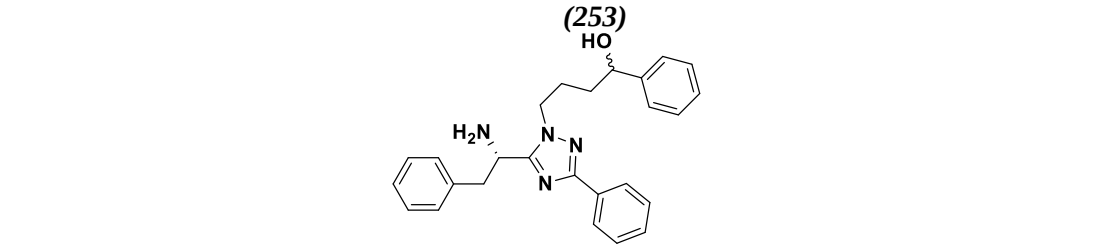
Benzyl (S)-(1-(1-(4-oxo-4-phenylbutyl)-3-phenyl-1H-1,2,4-triazol-5-yl)-2-henylethyl)carbamate (249)

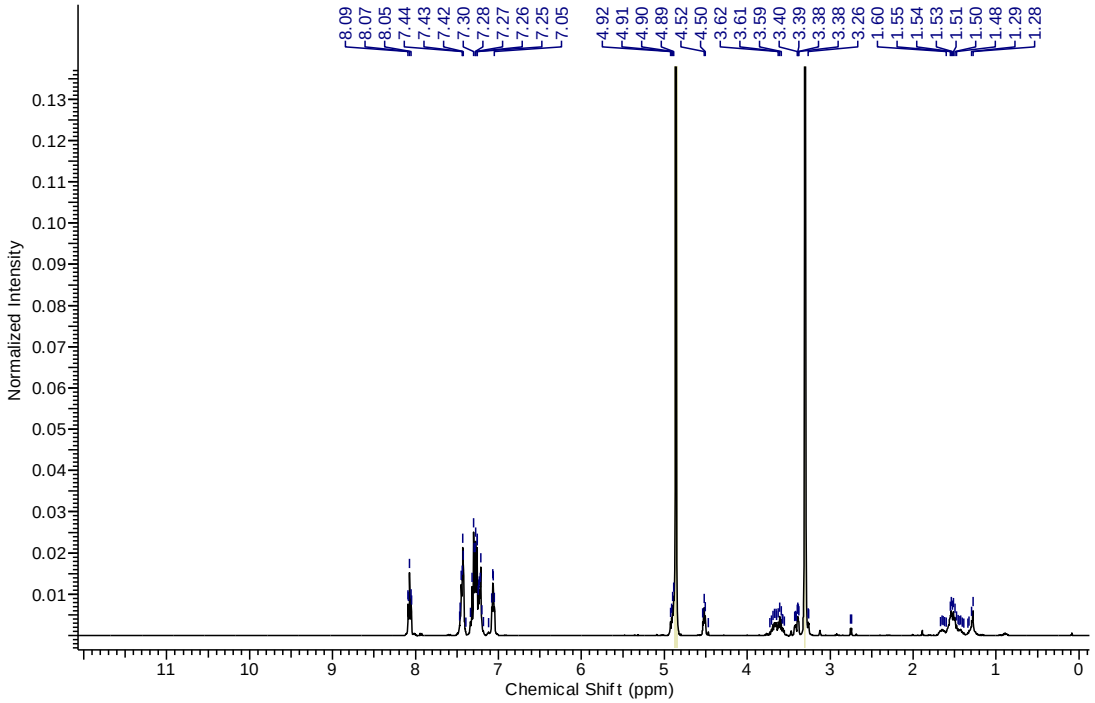


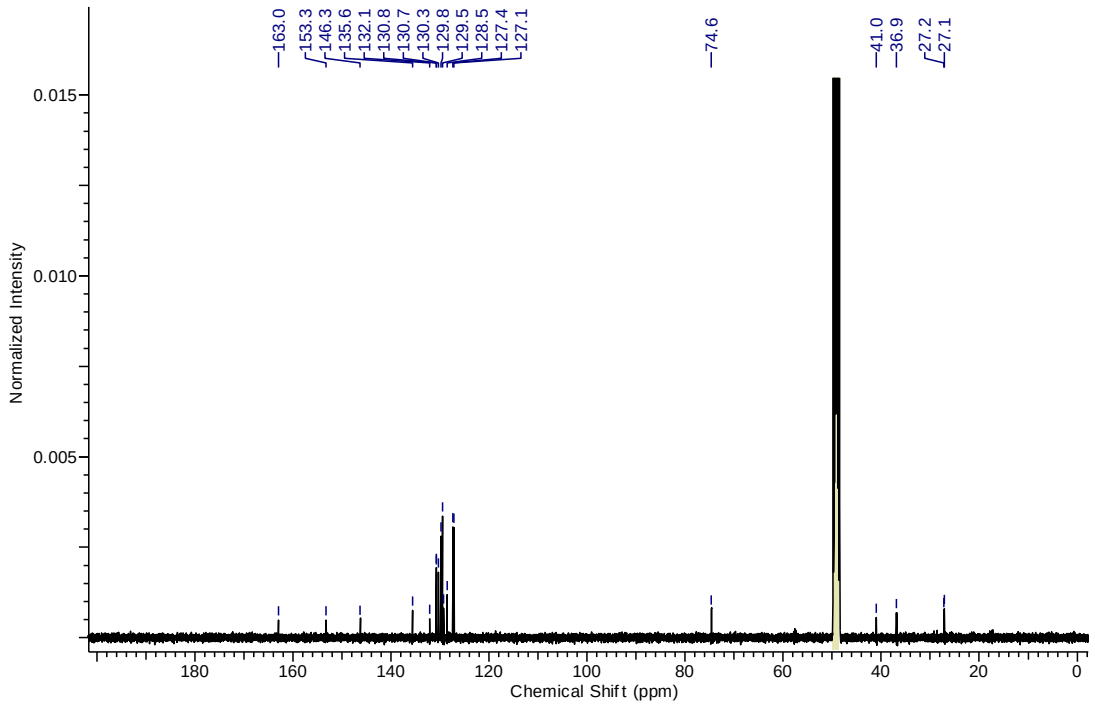


(S)-4-(5-((S)-1-amino-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-1-yl)-1-phenylbutan-1-ol

(253)

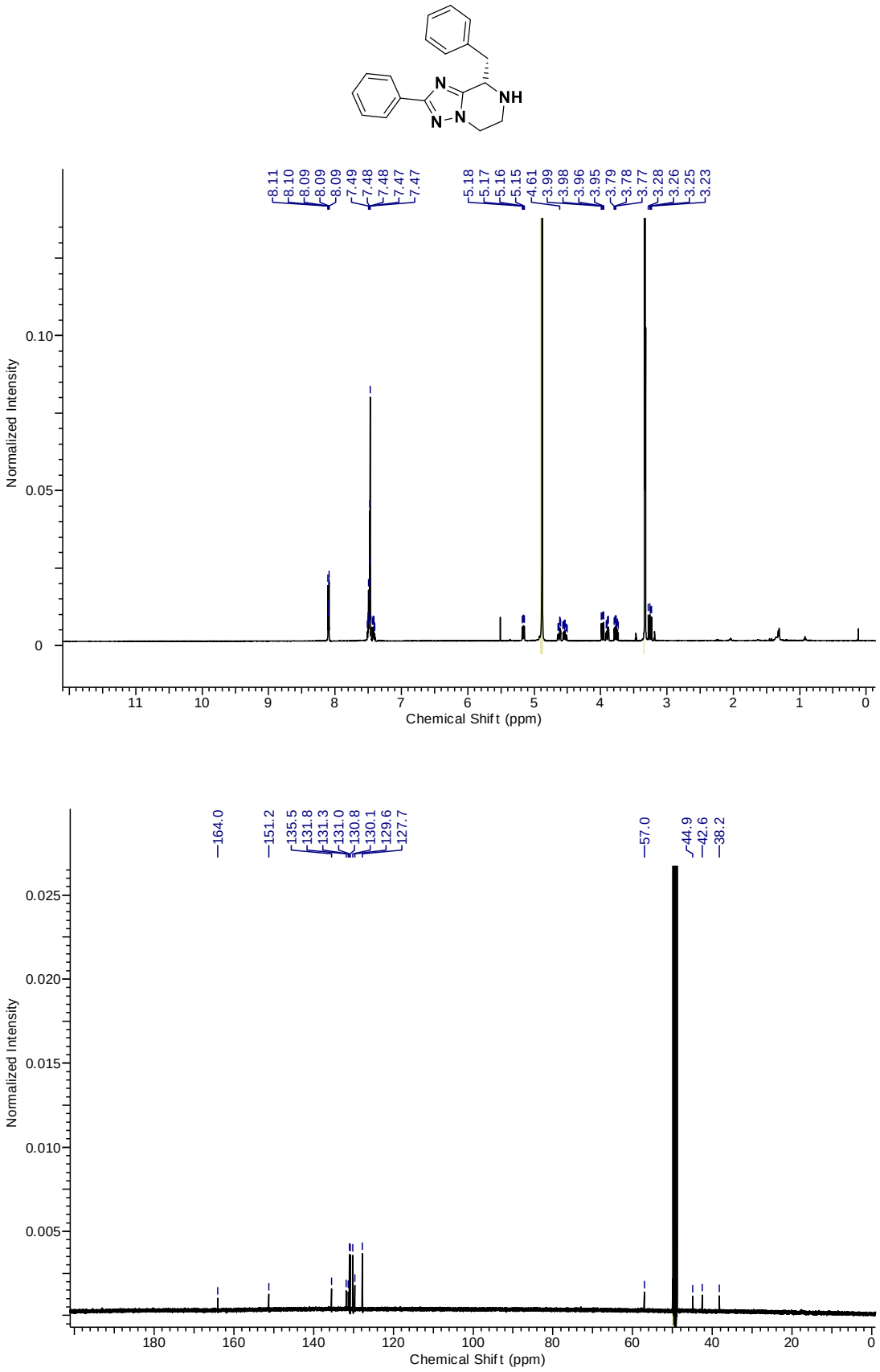




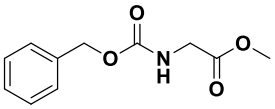


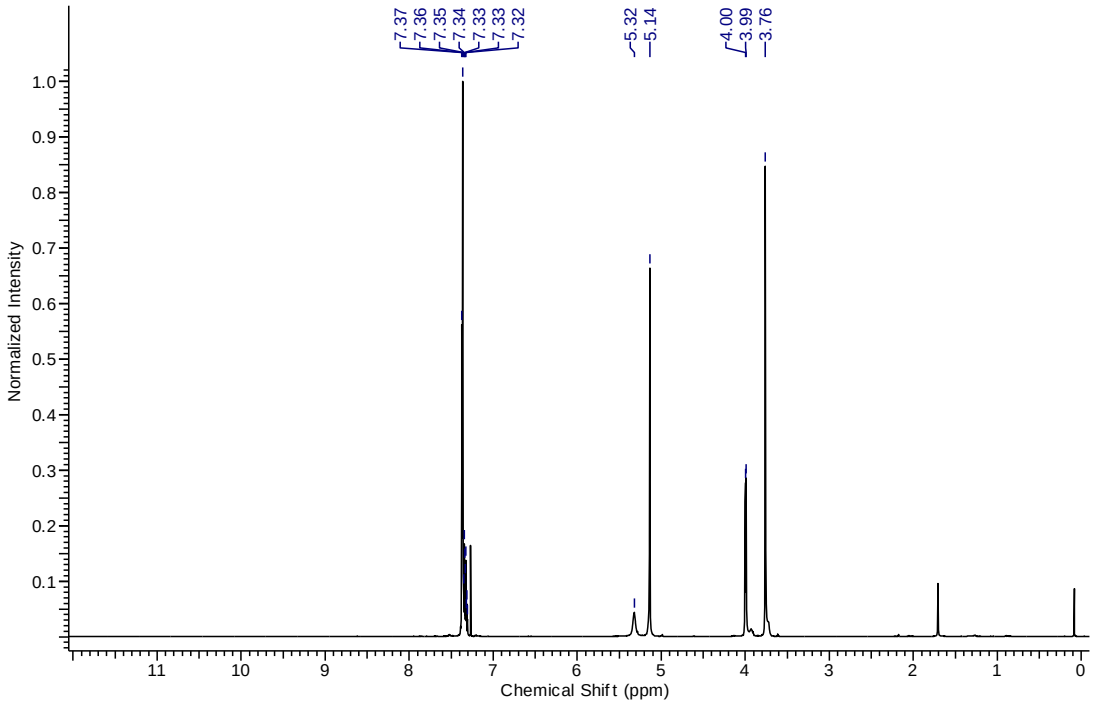
7.2.8. Single Chiral Centres

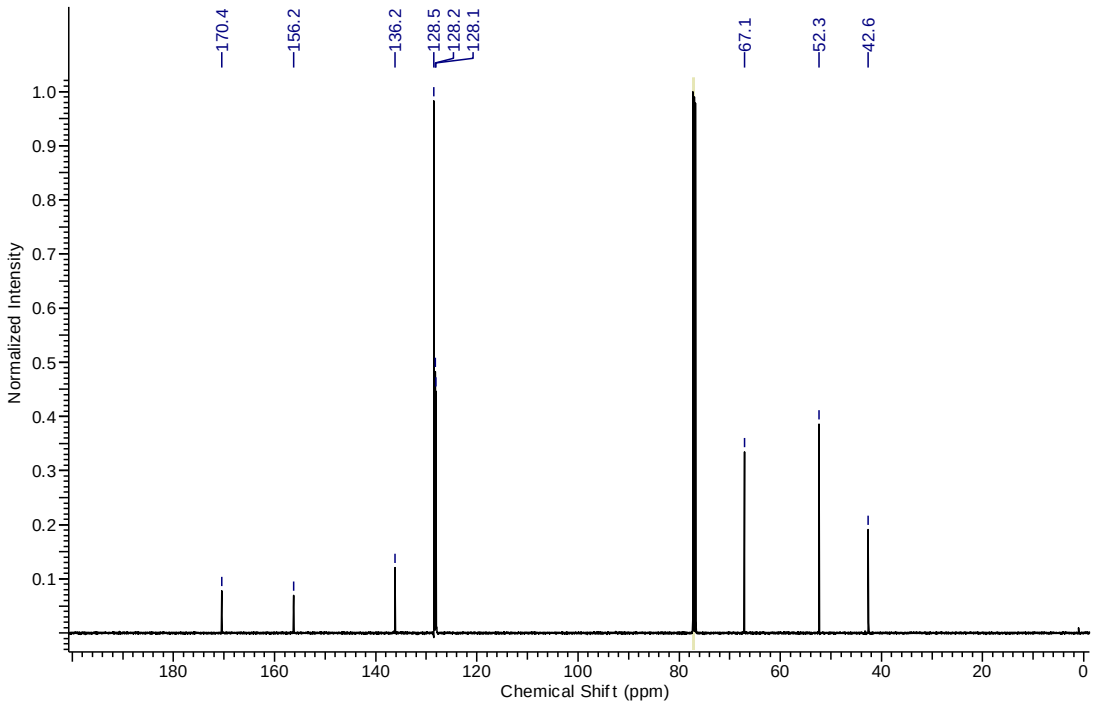
(S)-8-benzyl-2-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (172)



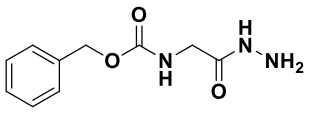
Methyl ((benzyloxy)carbonyl)glycinate (259)

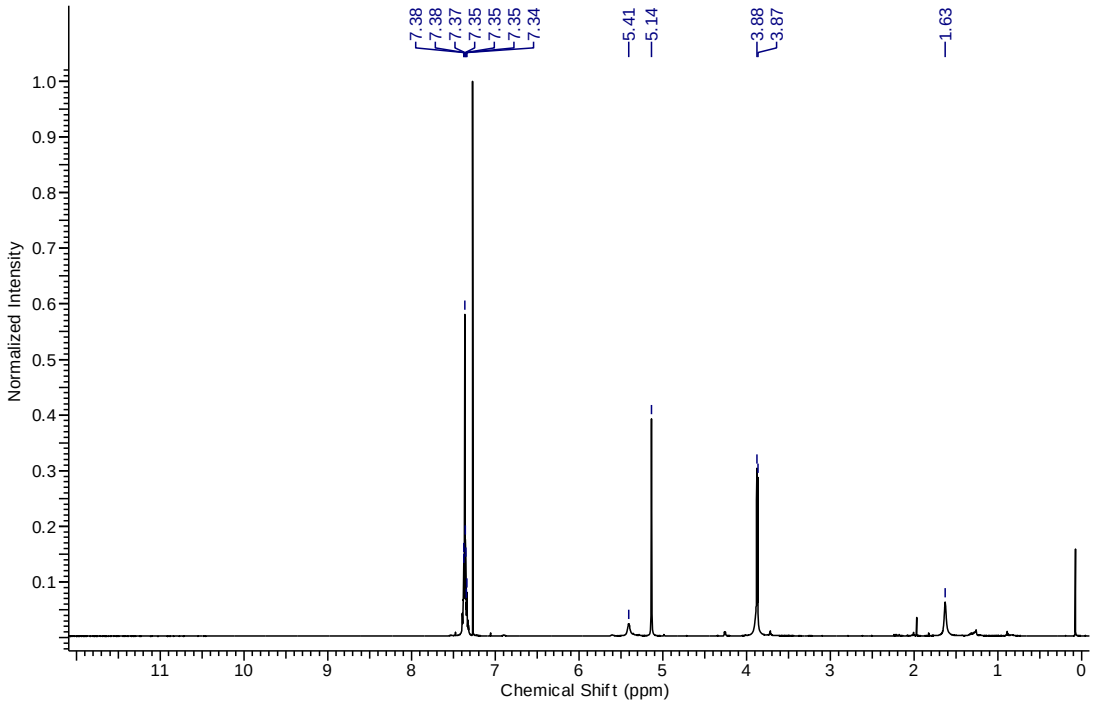


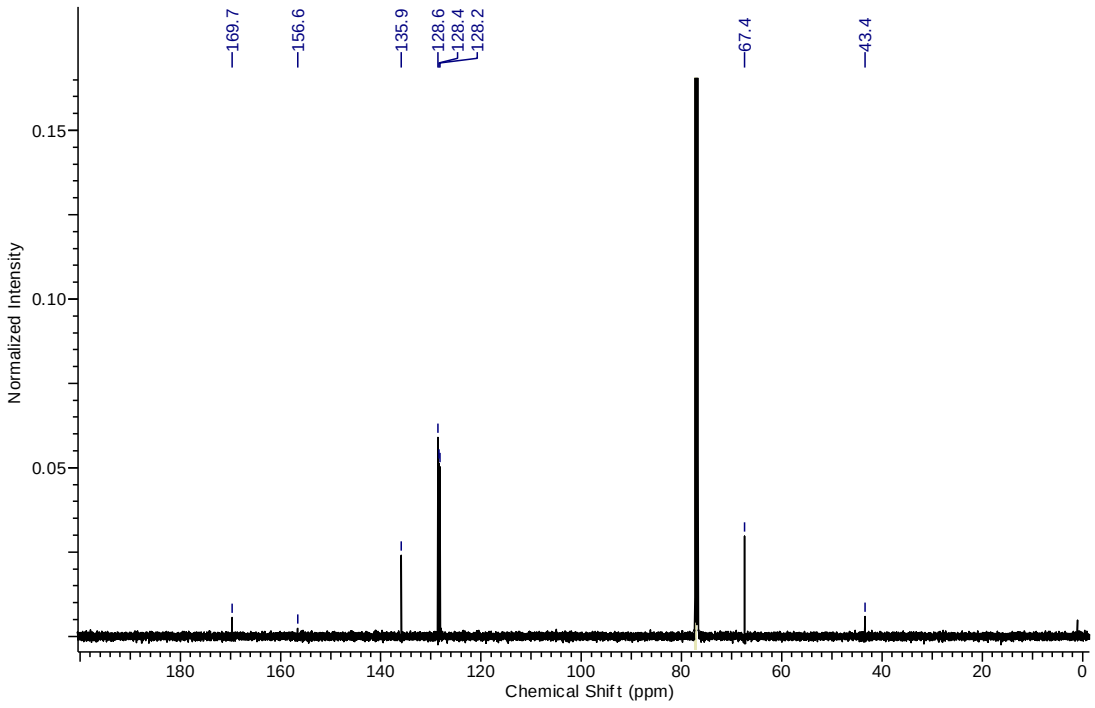




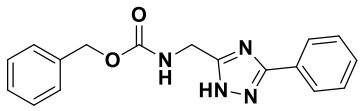
Benzyl (2-hydrazinyl-2-oxoethyl)carbamate (260)

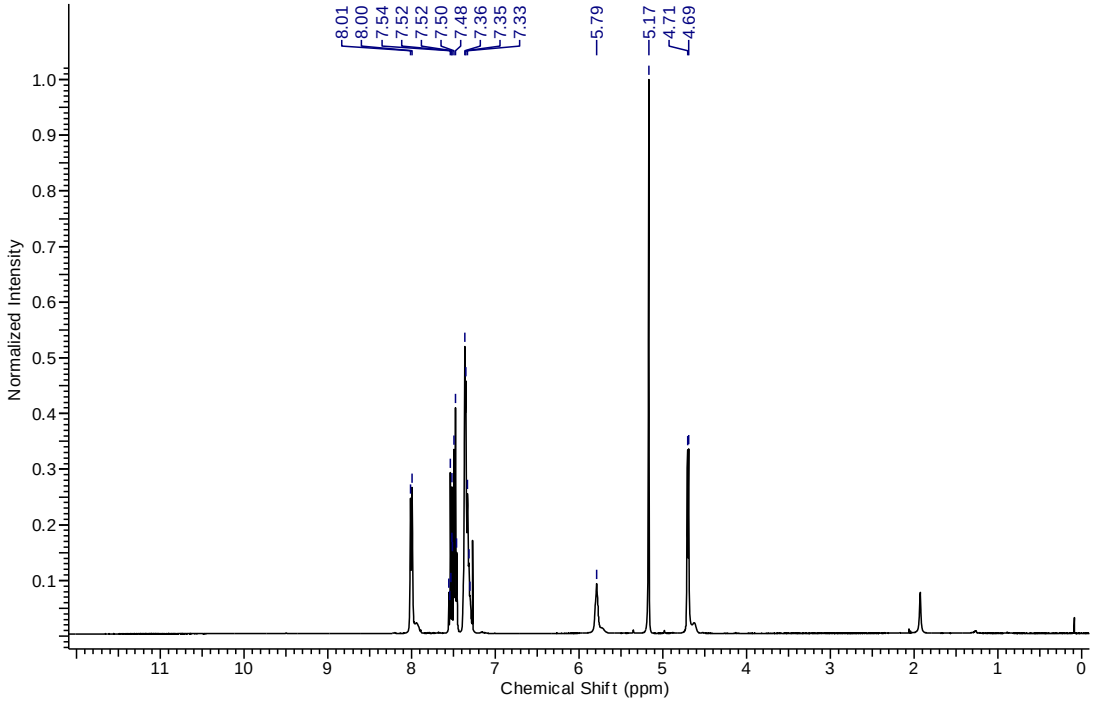


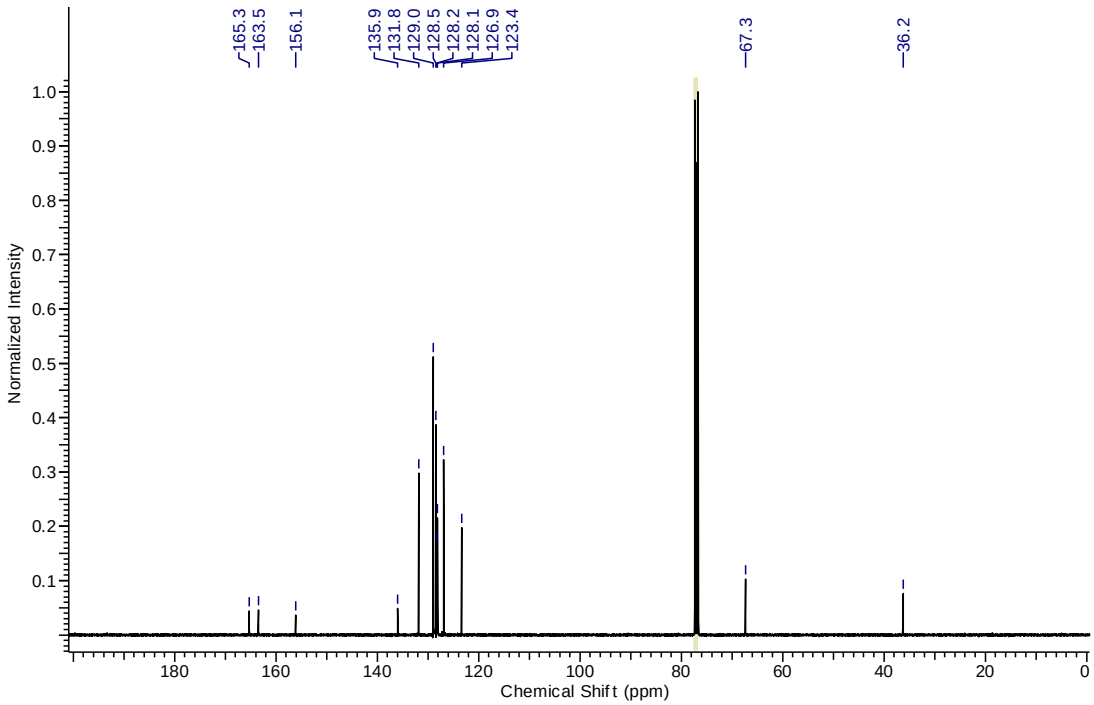




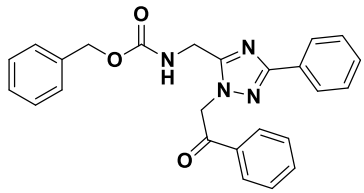
Benzyl ((3-phenyl-1H-1,2,4-triazol-5-yl)methyl)carbamate (261)

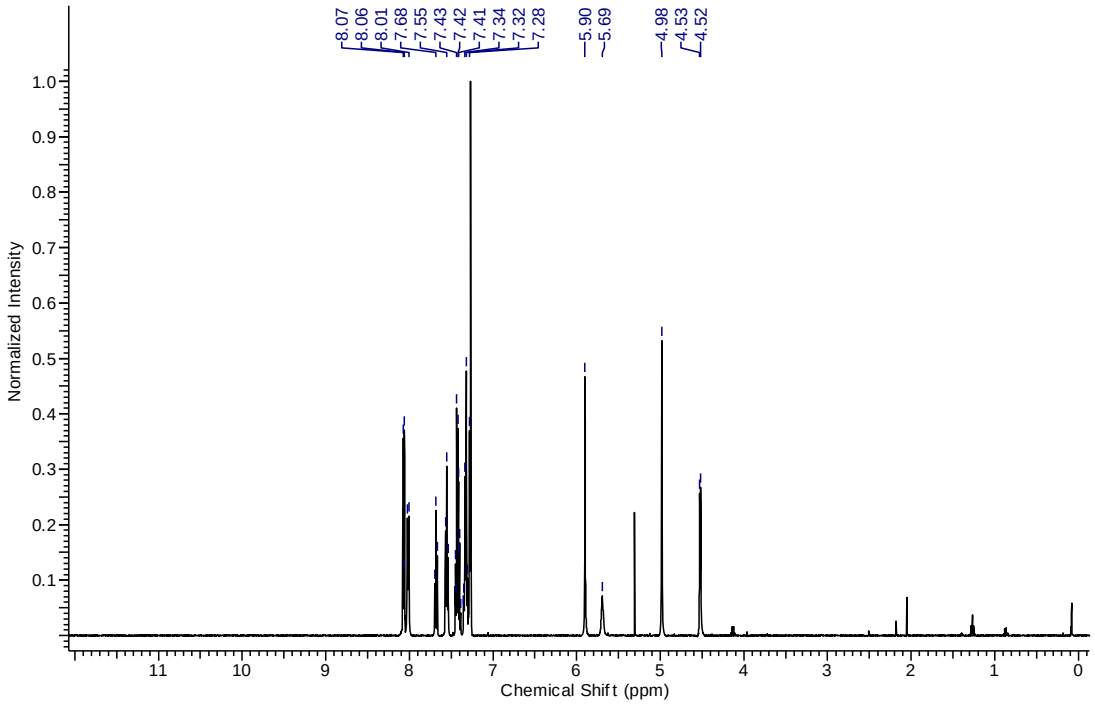


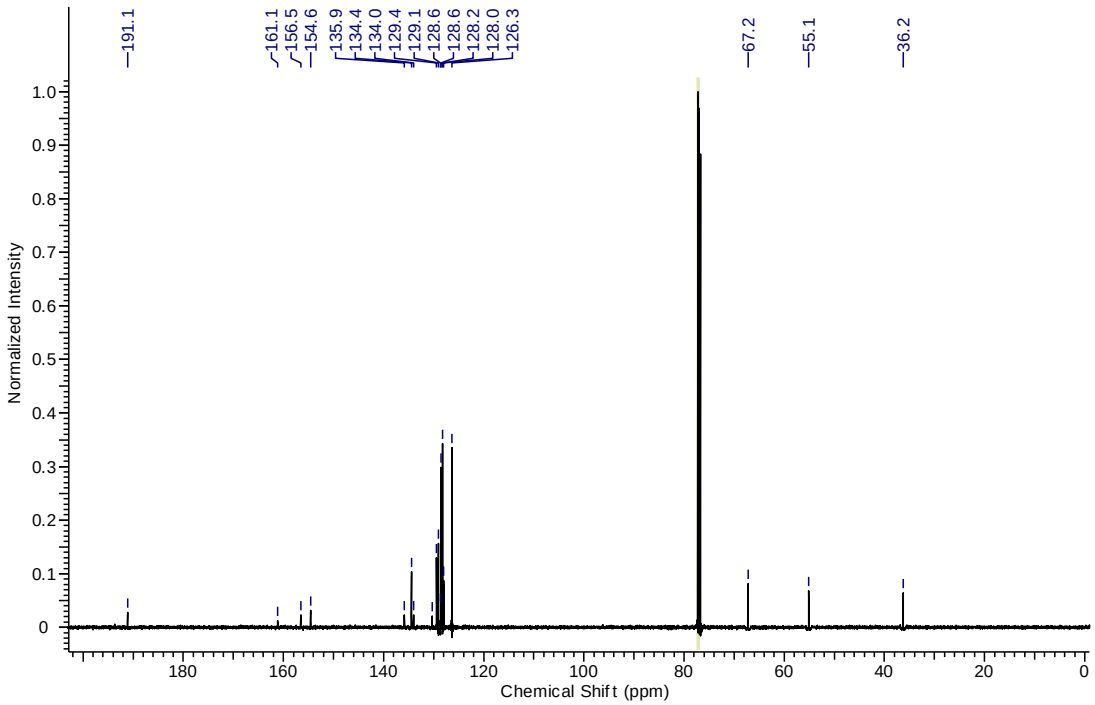




Benzyl ((1-(2-oxo-2-phenylethyl)-3-phenyl-1H-1,2,4-triazol-5-yl)methyl)carbamate (262)







2,6-diphenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (263)